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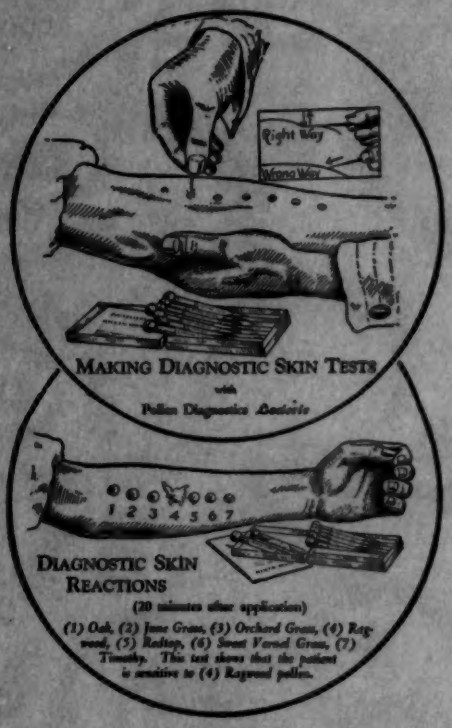

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ANNALS OF
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VOLUME 7 APRIL, 1934 NUMBER 10

SPLANCHNIC NERVE SECTION IN JUVENILE DIABETES

I. SELECTION OF CASES FOR OPERATION *

By GÉZA DE TAKATS, M.D., G. K. FENN, M.D., and RUTH A. TRUMP, B.S.,
Chicago, Illinois

THE present day conception of diabetes mellitus is that of a primary insulin deficiency, owing to lack of sufficient insulin production or secretion. Such teaching, naturally, places the pancreas in the center of interest. A clinically and pathologically proved type of such "pancreatic" type of diabetes is the one which follows an acute pancreatic necrosis with destruction of the islets and secondary cyst formation. One of us, with Mackenzie,[1] has followed up such cases with determinations of sugar tolerance. The diabetes in these patients is usually mild and, because of the marked regenerative power of the pancreas, the sugar tolerance may gradually return to normal.[2]

On the other hand, the careful histological studies of Warren Shields [3] failed to reveal any pathological changes in the islands in 27 per cent of 259 pancreases of diabetic individuals. The absence of abnormal changes in the pancreas is even more striking in the juvenile diabetic, where lymphocytic infiltration was the most characteristic lesion described by Warren Shields, and where irreversible changes seemed non-existent.

A few clinicians have attempted to make distinctions between various types of diabetes. Rudolph Schmidt [4] distinguished between a juvenile, asthenic, hypotensive individual, whose diabetes is pure hypoinsulinism, and a hypersthenic, hypertensive diabetic, who is producing enough or even too much insulin, but is over-compensated with mechanisms opposed to insulin. Seale Harris [5] expressed the view that during the natural course of diabetes an hyperinsulinic phase exists, which is later followed by hypoinsulinism.

Falta and his school [6] also recognize two types, one, which is readily compensated by insulin and in which withdrawal of insulin results in a marked glycosuria, polyuria and acidosis. This is the true insular type. The second type is more or less resistant to insulin. Massive doses of insulin are necessary and withdrawal of insulin does not strikingly affect

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the clinical picture. Of 74 cases studied, only 13 belonged to the first group. They believe in an extrapancreatic type of diabetes, where the counter-regulation to insulinic action is exaggerated.

This insulin-resistance has been further investigated by Depisch and Hasenöhrl.[7] They distinguished between two types of insulin resistance. The opposition to insulin may occur in the liver, or it may occur in the periphery. In the first case, the blood sugar curve following the administration of insulin is very shallow. In the second group, however, they obtained normal depression curves, but in determining both capillary and venous blood sugars, there was little if any capillary-venous difference. Priesel and Wagner[8] on the basis of an experience with 130 diabetic children, believe that children are practically never resistant to insulin, but there may be resistant stages of the disease.

Factors Influencing Insulin Sensitivity

From the above mentioned data, the importance of determining insulin sensitivity and the factors influencing it is perfectly obvious. While physiologists have been using the rough criterion of convulsive doses to estimate the effect of certain diets or operative procedures on insulin sensitivity, credit must be given to Csepai and Ernst[9] of the University of Budapest, who were the first to use small intravenous doses of insulin, calculated on body weight, to study the insulin sensitivity of patients with exophthalmic goiter. These authors gave 1/15 of a unit of insulin per kilogram body weight and avoided the subcutaneous route, to eliminate the disturbing factor of different rates of absorption.

The effect of *thyroid secretion* on insulin sensitivity has been investigated in the animal by Burn and Marks,[10] who found that thyroid feeding increased adrenalin-hyperglycemia until the liver glycogen was depleted. At that point the response to insulin became exaggerated. After thyroidectomy the sensitivity of dogs to insulin markedly increases, according to Aszódi and Ernst.[11]

The effect of pituitrin on insulin sensitivity was studied by Burn[12] who stated that injection of pituitary extract opposes the action of insulin. The extract was made of the posterior and intermediary part of the gland, whereas anterior lobe extracts did not alter the insulin hypoglycemia. Houssay and Magenta[13a] found that hypophysectomized animals became very sensitive to insulin. Recently Houssay has reported on the hyperglycemic effect of an alkaline extract of the anterior pituitary lobe.[13b]

Pancreatectomy was found to increase sensitivity to insulin by Aszódi and Ernst.[11] The pancreatectomized dog requires 0.065 unit of insulin per hour to maintain a normal blood sugar level, whereas the normal dog needs 0.25 unit of insulin (Holm, cit. by Bauer and Monguió[14]). Houssay, Lewis and Foglio (cit.[14]) found that 0.01 unit per kilogram per hour was the necessary amount of insulin that would maintain a normal blood sugar level in the pancreatectomized animal.

Adrenal denervation, or splanchnic section, increases insulin sensitivity.

The literature has been previously summarized.[15] With a quantitative test for insulin sensitivity, using 0.1 of a unit per kilogram body weight in the dog, Cuthbert and one of us found that celiac ganglionectomy,[16] adrenal denervation or splanchnic section [17] uniformly increased the response to insulin, while atropin or section of both vagi did not decrease this sensitivity.

The influence of *nutrition* on insulin hypoglycemia has long been recognized. Thus McCormick, MacLeod, Noble and O'Brien [18] stated that while the initial fall in blood sugar is not influenced by the glycogen content of the liver, glycogen-rich animals react faster to hypoglycemia. Rabbits with depleted liver glycogen were found to be more sensitive to insulin. This seems to be in disagreement with the work of Bainbridge [19] and Hynd and Rotter [20] who reduced the sensitivity of rats and mice to insulin by feeding them a carbohydrate-free, excess-fat diet. The latter authors found that such diets produced fatty livers and thus a resistance to insulin. Clear cut evidence of the important effect of diets upon alimentary hyperglycemia and insulin response in man was furnished by Himsworth,[21] who found that normal individuals are very much more sensitive to insulin on a high carbohydrate than on a high fat diet. Finally, Abderhalden and Wertheimer [22] stated that rabbits fed on an alkaline diet were much more sensitive to insulin than if they were fed on an acid diet.

The effect of heat was stated to increase insulin sensitivity by Krogh and Trevan and Boock (cit. Bainbridge [19]). Andrews [23] emphasized an increased sensitivity to insulin following dehydration.

To summarize the factors that influence insulin sensitivity in the animal we have tabulated the above mentioned references:

Insulin sensitivity is

Increased by		Decreased by	
Thyroidectomy,	Burn and Marks Aszódi and Ernst	*Thyroid feeding,*	Burn and Marks
Hypophysectomy,	Houssay and Magenta	*Pituitrin,*	Burn
Pancreatectomy,	Houssay, Lewis and Magenta Holm Aszódi and Ernst		
Celiac ganglionectomy,	de Takats and Cuthbert		
Adrenal denervation Splanchnic section			
High carbohydrate diet,	Bainbridge Hynd and Rotter Himsworth	*High fat diet,*	Bainbridge Hynd and Rotter Himsworth
Alkaline diet,	Abderhalden and Wertheimer	*Acid diet,*	Abderhalden and Wertheimer
Increased environmental temperature,	Krogh, Trevan and Boock		
Dehydration,	Andrews		

The clinical conditions that are known to increase the daily insulin requirement of the diabetic individual have been recently tabulated by Pollack [24] as follows:

1. Endocrine disturbances
   - Hyperthyroidism
   - Pituitary dyscrasias
   - Suprarenal dyscrasias
2. Hemachromatosis *
3. Hepatic disease
   - Cirrhosis *
   - Necrosis and infarcts
4. Lack of muscular tonus; debilitating states
5. Infection
6. Certain skin diseases
7. Circulatory decompensation
8. Antigenic properties of insulin
9. Fractures
10. Diabetic acidosis and coma
11. Possibly nervous mechanisms, relative either to the sympathetic system or to a center in the brain, which controls metabolism of sugar.

Obviously, when determining the insulin sensitivity of the normal or diabetic individual, these factors must be taken into account. It seems quite possible to us that most of the above mentioned conditions can be brought to a few common denominators as a cause for an increased insulin resistance. In none of these clinical conditions have insulin sensitivity determinations been made.

Method for Determining Insulin Sensitivity

In studying the effect of celiac ganglionectomy on the sugar tolerance of dogs, de Takats and Cuthbert [16] used 0.1 of a unit of insulin per kilogram body weight to determine the increase of insulin response following operation. This dose has been given in man a few times, but such a dose, or even a dose of 0.05 or 0.02 of a unit per kilogram body weight, may produce hypoglycemic symptoms so that the test has to be terminated by giving glucose. The dose of 0.01 of a unit of insulin per kilogram body weight is the minimal dose that seems to produce a small but consistent fall in the blood sugar curve of the normal individual. In the left column of figure 1, four such curves are charted. Bauer and Monguió [14] had pointed out that the threshold value of insulin, i.e., the minimal amount that would still affect blood sugar, varies a great deal, according to the constitution of the individual. This dose, however, that we have employed, seems to give a simple yardstick by which to measure the insulin sensitivity of diabetics. A few

* Contrary reports as to increased sensitivity to insulin are available.

of these are charted in the right column of figure 1. It is obvious that diabetics, generally speaking, are more sensitive to insulin than non-diabetics. This corresponds with the above quoted findings of Aszódi and Ernst, Holm, Houssay, Lewis and Foglio, that the pancreatectomized animal is much more sensitive to insulin and requires less insulin to maintain a nor-

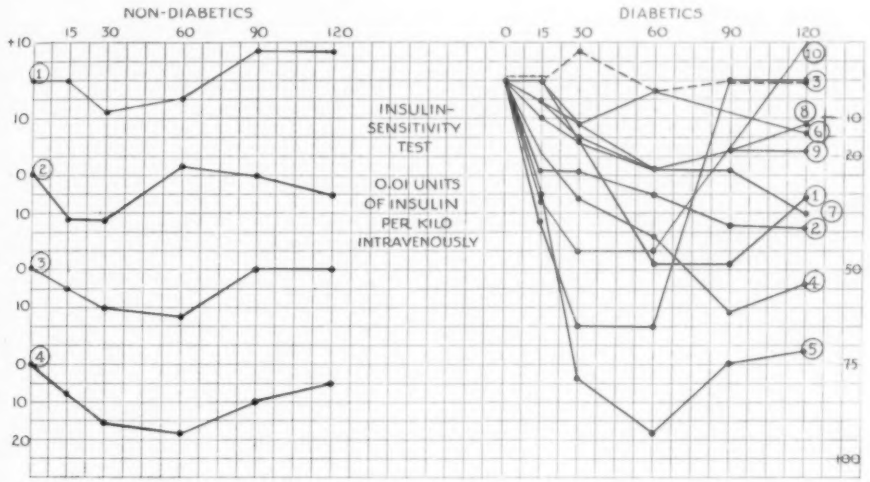

FIG. 1. Insulin sensitivity test. 0.01 unit of insulin was administered intravenously after a 12 hour fast. Blood sugars were determined with the micro-method of Folin-Wu before, and 15, 30, 60, 90 and 120 minutes after the injection. In the nondiabetic group (1) is Mrs. Theo., 62 year old woman, weighing 62 kg., with a chronic cholangitis; (2) is Mrs. Str., 45 year old woman, weighing 67.8 kg., with a luetic cardio-vascular system; (3) is Miss P., a 16 year old girl, weighing 70.3 kg., with hypothyroidism; and (4) is Mr. Ca., 25 year old male, with an old fracture of the astragalus. Of the diabetic group, (1) is Joe D., 16 year old severe diabetic boy; (2) is Margaret McCl., 11 year old diabetic girl, completely controlled, moderately severe diabetic; (3) is Frank Ha., 24 year old, severe diabetic male, with associated hyperthyroidism; (4) is Lois H., 10 year old girl with a mild, easily controllable diabetes; (5) is Richard B., 14 year old, severe, very unstable diabetic, with suggestive symptoms of hypopituitarism; (6) is Mrs. Elsie C., 30 year old, married woman, with mild diabetes following acute pancreatic necrosis; and (7) is Alvin W., 22 year old, diabetic boy, a few weeks after diabetic coma. Note the absence of a rise in the blood sugar level at the end of two hours; (8) is Hattie M., 42 year old woman with mild diabetes, and a sinus infection; (9) is Mrs. V. H., mild, well controlled diabetic; and (10) is Joe Sch., 19 year old, severe diabetic, with seemingly excessive counter-regulation to insulin. The interrupted line in the diabetic group represents the blood sugar level of Joe D. (1), without any insulin, to illustrate that the fall in blood sugar is not due to the two hour fast; note that in the nondiabetic group the dose of 0.01 unit of insulin per kilo barely lowers the blood sugar level, which is always back to normal in two hours. In the diabetic group the action of insulin is much more pronounced, and with the exception of case 3, complicated by hyperthyroidism, and case 10, the blood sugars are far below the original level after two hours. Diabetics, generally speaking, are more sensitive to insulin than nondiabetics.

mal blood sugar than the normal one. The initial, fasting blood sugars have been brought to a common zero level in the first figure.

The test is carried out as follows: A fasting blood sugar is determined from capillary blood, using the modified micro-method of Folin-Wu. Insulin is injected intravenously, using 0.01 unit of insulin per kilogram body weight. Blood sugars are determined 15, 30, 60, 90 and 120 minutes

after the injection. The patient is kept quiet during this time, preferably lying on a couch, in a room of even, non-extreme temperature. Excitement, fear or infection of any sort may vitiate the results. The diet should not be excessive in carbohydrate or fat.

When the insulin curves of 10 diabetics, shown in figure 1, are charted on the basis of actual blood sugar values (figure 2), it becomes obvious that the initial blood sugar level has a great deal to do with the steepness of the

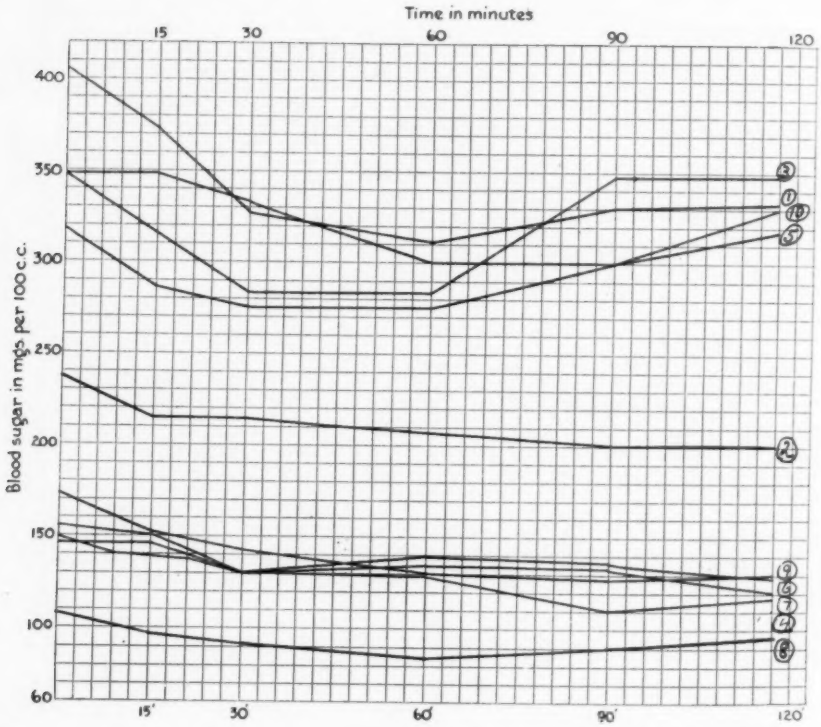

FIG. 2. Insulin sensitivity curves of 10 diabetic patients. The curves have been plotted on the base of the actual figures. Note that the curves with fasting blood sugars between 300 and 400 mg. per 100 c.c. show greater fluctuation than the curves with an initial value between 100 and 200 mg. The only curve between 200 and 300 mg. takes an intermediate position between the two groups. Case numbers as in figure 1.

depression-curve and also with the rapidity of return to the previous level. Thus it will be noted that curves 1, 3, 5 and 10, whose fasting blood sugar value is between 300 and 400 milligrams of sugar, show much greater fluctuations of the blood sugar level than curves 4, 6, 7, and 9, whose fasting blood sugars are between 100 and 170 milligrams of dextrose. That, however, the curve may be constant within reasonable limits (120–170 milligrams), is shown in figure 3 of a 10 year old diabetic girl, Lois H., whose insulin curves are almost identical, whether the fasting blood sugar was 173 mg. or 118 mg.

It is desirable, then, to bring down the fasting blood sugar level to 170 milligrams or less, before determining the insulin sensitivity curve. When, however, an insulin resistant curve is obtained on a patient, whose fasting blood sugar is above 200 milligrams per 100 c.c. of blood, the anti-insulinic action is all the more obvious.

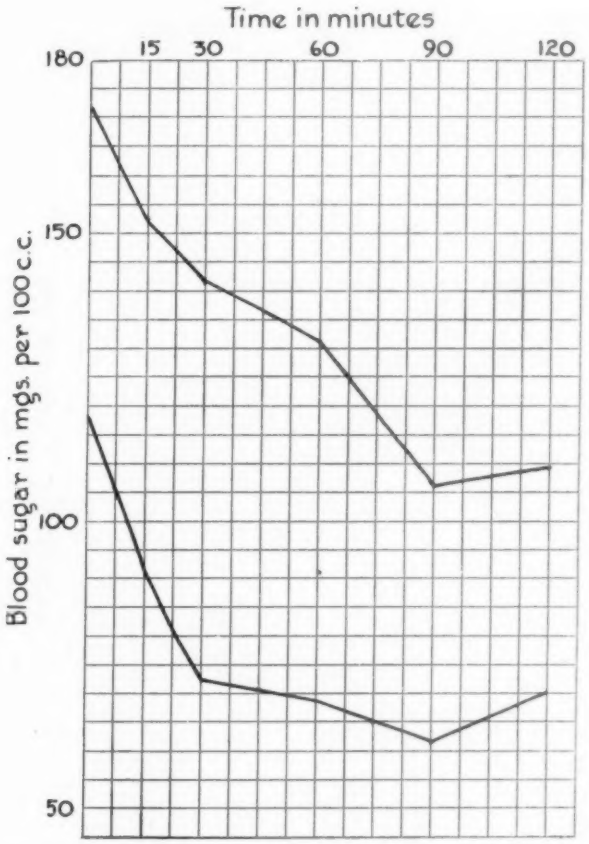

FIG. 3. Insulin sensitivity curve starting from different fasting levels (Lois H.) In spite of the different initial figures (118–172 mg.) the two insulin sensitivity curves are almost identical.

It was naturally the insulin resistant group that we were interested in, as there was a possibility, on the basis of our previous animal experiments, that one might make these patients insulin sensitive. The case report of the first such relatively resistant diabetic, who was rendered insulin sensitive by bilateral splanchnic section, has been previously published.[25]

The resistance or opposition to the action of insulin may be further elucidated by the study of the difference of capillary and venous blood sugars following the administration of insulin. The capillary blood sugar is identical with arterial blood sugar. The arteriovenous difference in blood

sugar, as pointed out by Foster,[26] Frank, Nothmann and Wagner,[27] Lundsgaard and Holbøll,[28] Lawrence, [29] Rabinovitch [30] and Himsworth,[21] indicates the activity of insulin in the tissues. The drop in venous blood sugar compared with the capillary blood sugar is particularly marked after a fat poor, high carbohydrate diet, as shown by Depisch and Hasenöhrl [7] and Himsworth.[21] We have not made extensive use of this method, but wish to show a few curves (figure 4) illustrating that the insulin resistant diabetic may

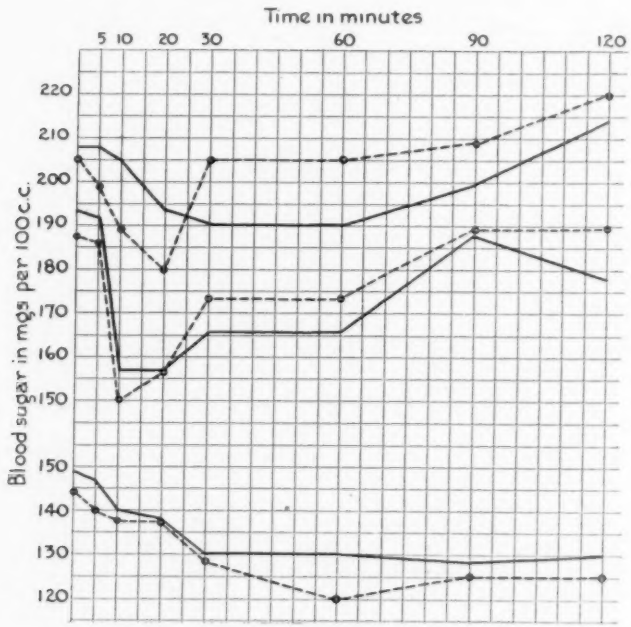

FIG. 4. Capillary venous differences in blood sugar following the administration of insulin. Straight lines, capillary blood sugar curves; interrupted lines, venous blood sugar curves. Upper row: Frank Ha., severe juvenile diabetic, insulin sensitivity test without ergot. Middle row: Same patient, insulin sensitivity with two doses of ergot, as in the galactose-ergot test. This patient's insulin resistance must be in the periphery. Ergot improved the primary fall in blood sugar, and diminished the peripheral rise in venous sugar. Lower row: Insulin curve of Mrs. H., mild diabetic. Peripheral action of insulin is marked.

even show a higher venous than capillary blood sugar, indicating that the insulin opposing mechanism can mobilize sugar from the periphery. Ergot made case 1 more sensitive to insulin and diminished the opposition in the periphery.

THE ERGOTAMINE RESPONSE

A complete review of the chemical and pharmacological properties of ergot is found in Barger's monograph.[31] Barger and Dale have shown that ergotamine reverses many actions of epinephrin, all of the excitatory and some of the inhibiting effects. Ergot reverses the action of epinephrin on

melanophores,[32] sensitizes the vagus [31] and increases tissue oxidation.[33] A complete bibliography of the effect of ergotamine on carbohydrate metabolism is given by Tada.[34]

Several authors have studied the effect of ergot on alimentary hyperglycemia. The literature is summarized in the work of Wachsmuth and Loeweneck,[35] who found that alimentary hyperglycemia can be almost com-

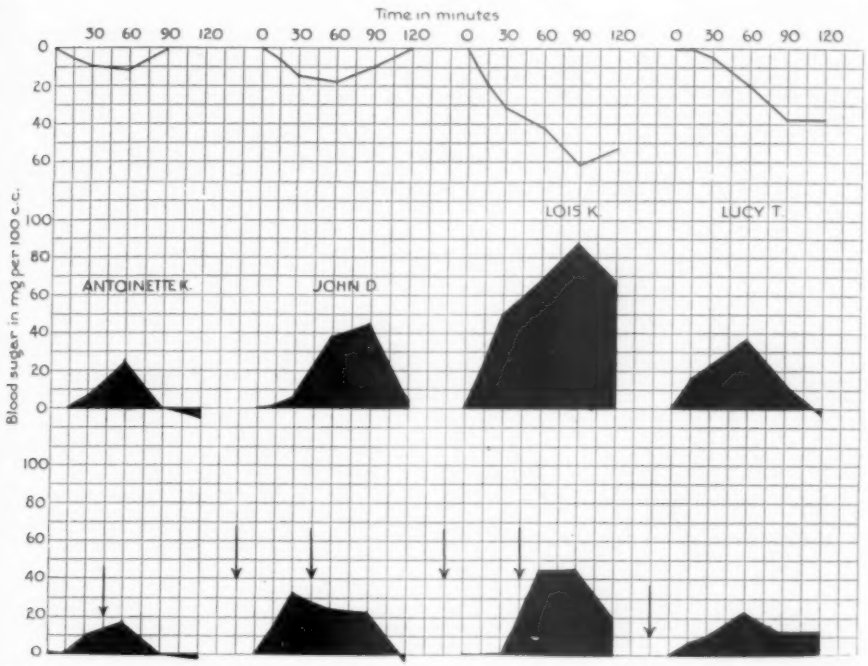

FIG. 5. Upper row: Insulin sensitivity test. Dosage and time of blood sugar determinations as in figure 1. Middle row: Blood sugar curves following the oral administration of 40 grams of Pfanstiehl's pure d. galactose in 250 cubic centimeters of water. Lower row: Same amount of galactose was given with 0.1 of a cubic centimeter of "Gynergen" (Sandoz) per every 10 kilograms of body weight. The ergot preparation was injected 15 minutes before the administration of galactose and the dose repeated one hour later. In the early experiments 1 cubic centimeter of "Gynergen" was given, regardless of weight, only once, 15 minutes before the galactose. The arrows indicate the injection of ergot. Antoinette K., 38 year old, nondiabetic woman, with polyarthritis. John Duz., 36 year old male, nondiabetic, with rheumatic heart disease. Lois K., 10 year old, diabetic girl, on a diet of 135 gm. glucose with 10 units of insulin once a day. She was fairly stable, easily controllable. Lucy Tra., 45 year old woman, with mild diabetes, which became manifest after a hysterectomy. She was sugar free on a restricted diet without insulin. With the exception of Lois K., the galactose causes little rise in the total blood sugar. The ergot produces slight depression in these curves.

pletely suppressed in the animal by a combination of ergot and atropin. The small residual hyperglycemia was explained as due to absorption from the intestine. The main rise was due to a secretion of sugar from the liver, which could be inhibited by ergot and atropin. These drugs did not act by altering intestinal absorption, as indigocarmin, fed by mouth, appeared without delay in the blood stream. Lawrence,[36] on the other hand, while

obtaining almost complete suppression of the alimentary hyperglycemia with ergotamine in man, explained this by the delay of the ingested carbohydrate in the stomach.

To produce alimentary hyperglycemia, Pollak and his coworkers [37, 38] used galactose instead of dextrose. They stated that the galactose tolerance of the diabetic patient was not diminished. This was also found to be true

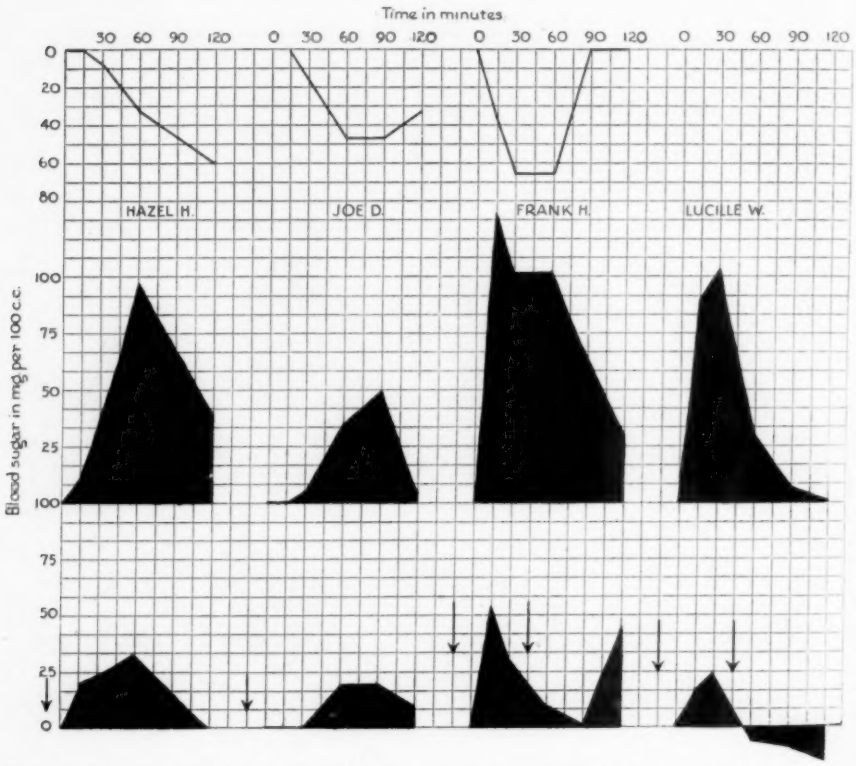

FIG. 6. Insulin sensitivity tests and galactose-hyperglycemia curves with and without ergot as in figure 5. Arrows indicate the administration of ergot. Hazel H., 16 year old, diabetic girl, fairly sensitive to insulin, shows a marked increase in blood sugar following galactose, which is well suppressed to a normal curve following ergot, although only one dose of ergot was given. Joe D., 15 year old, severe diabetic boy, with moderate response to insulin, shows a fair response to ergot after one dose. Frank H., 26 year old, severe diabetic, with hyperthyroidism and repeated attacks of acidosis. Lucille W., 28 year old woman with a diabetic tolerance curve, but sugar free on a non-restricted diet, and a normal metabolic rate. Note the marked response of the galactose-hyperglycemia curve to ergot.

by Roe and Schwartzman [39]; and yet a marked hyperglycemia follows the administration of galactose in some diabetics, which these authors explained by a more rapid conversion of galactose to dextrose. Pollak and his coworkers stated that it was possible to suppress this increased gluconeogenesis by ergot and atropin in one group of diabetics.

Mager [40] has published a number of galactose hyperglycemia curves on normal and hyperthyroid patients. The curves of the latter were much

higher, indicating that glycogen fixation in the hyperthyroid group is much more unstable.

When we consider that galactose is converted to dextrose only in the liver, that it is practically not utilizable by any other tissue than the liver, and that after it reaches the circulation it is excreted in the urine, regardless of kidney or endocrine dysfunction (Shay, Schloss and Bell,[41]) it appears that we are in possession of an ideal substance, the conversion of which into dextrose and its suppression by ergot may give an indication of the intensity of sugar mobilization from the liver, and the action of a sympathico-adrenal depressant on it. Our graphs indicate that the ergotamine response in normal individuals and some diabetics is small, whereas in diabetics showing a marked hyperglycemia following the administration of galactose, the suppression is definite (Hazel, Frank, Lucille). (Figures 5 and 6.)

Our technic is as follows: A fasting blood sugar is determined by the modified micro-method of Folin-Wu and the individual is given 0.1 of a c.c. of gynergen (Sandoz) for every 10 kilograms of body weight, subcutaneously. Fifteen minutes later, 40 grams of galactose (Pfanstiehl's pure d.) is given by mouth in 250 c.c. of water, flavored with a little lemon juice. Blood sugars are taken at 15, 30, 60, 90 and 120 minutes after the ingestion of the galactose. A second dose of the same amount of gynergen is given one hour after the first dose. Prior to this test, a few days before, a galactose tolerance curve is determined with the same technic, but without the ergot.

The Value of These Tests Regarding Operability

In presenting the few data at our disposal, it was not our aim to evaluate the merits of the insulin and ergotamine tests in the study of diabetes. This we hope others will do on a larger clinical material. Our sole concern was to establish certain data which would suggest that a splanchnic section in a given case of juvenile diabetes might be of benefit. One of us, with Cuthbert,[16, 17] has shown that celiac ganglionectomy, splanchnic section or adrenal denervation are all capable of increasing sugar tolerance and increasing insulin sensitivity. Thus our immediate aim in operating on diabetics was to make them more sensitive to insulin, if they were insulin-resistant.

This "insulin-resistance" should not be interpreted as similar to that present in those rare cases reported in the literature, in which from 600–1000 units of insulin were given to diabetic patients, mostly in coma, without effecting any lowering of blood sugar. Such insulin resistance seldom occurs in children.[8] The insulin resistance in our nomenclature is manifested by an insulin depression curve, following a minimal dose of insulin, which in the well controlled, possibly sugar free, otherwise healthy diabetic, is unusually flat, and does not show the dip of 40–60 milligrams of blood sugar, shown in figure 1. We have carefully enumerated the factors that will influence insulin-sensitivity, and in interpreting these curves, the effect of

diet, nutritional state, thyroid or pituitary dysfunction, infection and acidosis should certainly be considered.

But a more direct attempt to imitate the effect of splanchnic section is the galactose-ergot test. The fact that ergot diminishes the galactose-hyperglycemia in a certain group of diabetics is shown in our graphs. This effect may be due to a more rapid oxidation of dextrose in the periphery under the action of ergot or to a decreased conversion of galactose to dextrose in the liver as a result of inhibiting sympathetic, glycosecretory impulses, or, finally, as Pollak and Selinger [37] suggest, to an increase of retention and fixation of glycogen (glycopexy). To us it seems as if a complete reversal of epinephrin action had taken place; and thus this method serves as an indication of the effect of sympathico-adrenal exclusion on the carbohydrate metabolism. Recently, in a series of articles from Cannon's laboratories, Schlossberg, Sawyer, and Bixby [42] showed that homeostasis is similarly affected in sympathectomized animals as in ergotaminized ones. We feel that the temporary ergotaminization of the patient gives a good indication as to the effect of splanchnic section on carbohyrate metabolism. The assumption of Lawrence [36] that ergotamine cannot be used for this purpose because it delays absorption by prolonging the emptying time of the stomach has not been confirmed. One of our diabetic patients, who showed a marked suppression of the galactose hyperglycemia with ergot, showed no change in the emptying time of the stomach after ergot. The barium, however, was markedly delayed in the small intestine, which, if anything, would result in a higher glycemia curve, as absorption of glucose occurs mostly from the small bowel.

An even more direct imitation of the surgical procedure is the paravertebral block with novocain, as the splanchnic nerve or its origin from the dorsal sympathetic ganglia may be temporarily blocked. Popper and Hirschhorn [43, 44, 45] have blocked the eighth, ninth and tenth dorsal sympathetic ganglia on the right side with novocain and obtained a decrease in galactosuria in early cases of cirrhosis, a flattening of the alimentary hyperglycemic curve and a marked effect on the protein metabolism of the liver. In our limited experience, however, the discomfort and often pain which accompanies such paravertebral injections markedly raises blood sugar in the emotionally unstable diabetics, and we have abandoned this method of ascertaining the effect of future splanchnic section.

In previous communications it has been stated that the severe type of juvenile diabetic, with unstable tolerance, and one that has been diabetic for at least two years and adequately controlled for several months before the proposed operation, and one that shows no detectable vascular damage by films of peripheral vessels and ophthalmoscopy, is the type in which operative procedure to improve carbohydrate metabolism could be undertaken with hope of benefit. To this we may now add that such a patient should be resistant to insulin and respond to ergot, if we are to accomplish anything with an operation on the sympathetic nervous system. Thus our

first patient operated upon showed an increased sensitivity to insulin following operation, which she still maintains 10 months after the operation (figure 7). Her galactose tolerance curve after the operation is not unlike the one before operation, when ergot was simultaneously administered

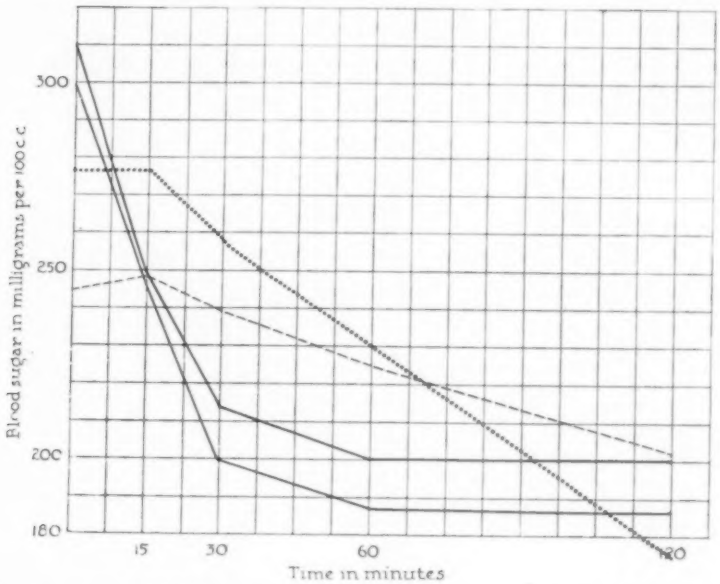

FIG. 7. Insulin sensitivity curves of case 1 before, immediately after, and 12 months after bilateral splanchnic section. Interrupted line, before operation; straight lines, one and two months after operation; dotted line, 12 months after operation.

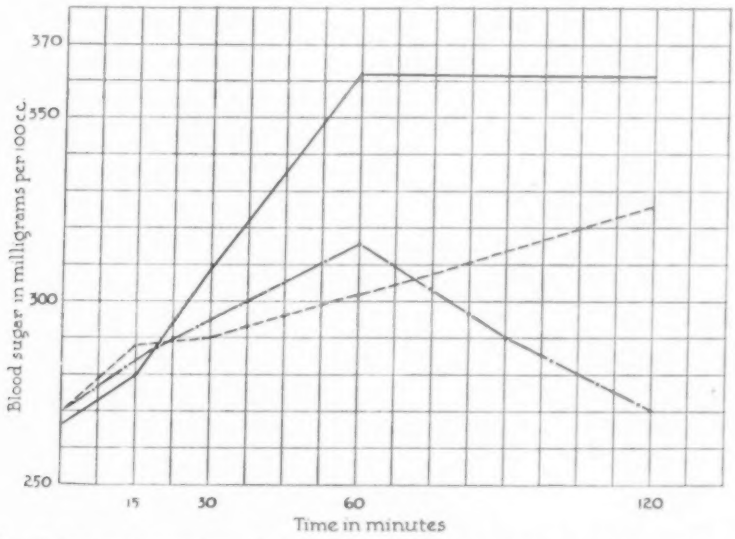

FIG. 8. Galactose hyperglycemia in case 1, before and after splanchnic section. Straight line, galactose hyperglycemia without ergot; interrupted line, galactose hyperglycemia with ergot, both before operation; line and dot, galactose hyperglycemia without ergot after operation.

(figure 8). In contrast, figure 9 of the second child operated upon, who was not resistant to insulin and whose galactose hyperglycemia was not very high and not greatly influenced by ergot, shows that splanchnic section did not influence the insulin sensitivity, and that the galactose curve has not been depressed. Ergot now shows a reversal of its usual effect, a true epinephrin effect. Nothing can be gained by splanchnic section in this type of case and it emphasizes the importance of the above discussed two tests in the selection of cases for operation.

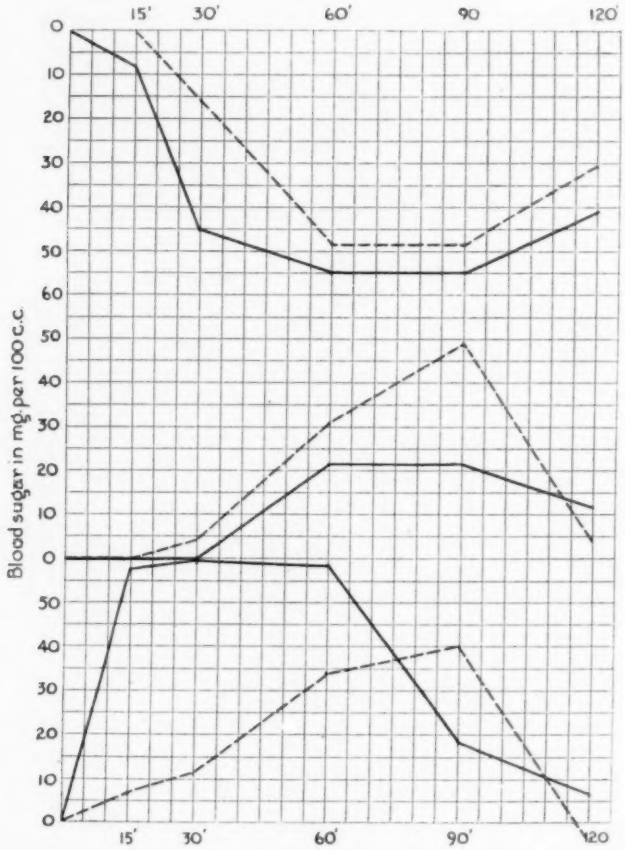

FIG. 9. Insulin sensitivity and the galactose-ergot test in case 2, before and after splanchnic section. Upper row: insulin sensitivity test; interrupted line, before; straight line, after the operation. Middle row: galactose hyperglycemia before and after operation. Lower row: galactose hyperglycemia with ergot, before and after operation. Interrupted lines, before; straight lines, after the operation.

SUMMARY

For the study of diabetes mellitus, particularly of the uncomplicated. juvenile type, two tests are described. The first determines the insulin sensitivity of the patient following the intravenous administration of a small

dose of insulin, calculated on body weight. This test differentiates insulin-sensitive from insulin-resistant diabetics. The factors that influence insulin response are discussed. The second test, namely, the effect of ergotamine on galactose-hyperglycemia, again separates diabetics whose alimentary hyperglycemia can be readily diminished by a sympathetic depressant, from another group, in which this drug had hardly any effect. Whether this means actually two types, a pancreatic and an extra-pancreatic type of diabetes, is an open question. But the group which is insulin resistant and sensitive to ergot offers hope that splanchnic nerve section may beneficially inhibit the forces that oppose insulinic action.

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A CONSIDERATION OF THE GASTRIC ULCER-CANCER PROBLEM

WITH THE REPORT OF A CASE OF ULCERATING CARCINOMA IN WHICH THE GASTRIC ACIDITY CHANGED FROM NORMAL TO ANACIDITY WHILE UNDER OBSERVATION *

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A RECENT editorial,[1] "Gastric Cancer and Ulcer," in *The Journal of the American Medical Association*, has this final paragraph:

> . . . it would seem that the question of the percentage of gastric ulcers becoming malignant is purely academic, and the most important and practical issue underlying the whole problem is that there are no known criteria by which the clinician, the roentgenologist or the surgeon can decide definitely the exact nature of a given ulcer. Microscopic examination alone will reveal its true nature. The patient cares little whether he has a primary carcinomatous ulcer or a carcinoma-on-ulcer but is vitally interested in knowing whether his gastric ulcer is benign or malignant. If this cannot be determined by clinical methods it is important that the nature of the ulcer be established microscopically at a time when the benefit of early surgical treatment of eventual gastric cancer can still be secured.

We were prompted to consider this problem largely because we were unable to agree with this note of extreme pessimism. Yet when we remember, (1) that about one of every 20 persons dying after 40 years of age does so because of cancer of the stomach; (2) that cancer of this organ accounts for about one-third of all deaths from cancer; (3) that the incidence of cancer is on the increase; (4) that in spite of all the education broadcast emphasizing the importance of an early diagnosis of cancer, it is doubtful whether physicians see gastric carcinoma early enough to produce a cure in more than from 1 to 2 per cent of the cases; and (5) that medical opinion at various times has considered gastric ulcer the precursor of gastric cancer in 60 per cent or more of the cases, it cannot be denied that some pessimism is justifiable. On the other hand, however, when we remember (1) the opinion of Gregory Cole (in which we concur) that simple gastric ulcer may readily be healed by medical treatment; (2) that medical opinion is rapidly becoming convinced that subtotal gastrectomy is the operation of choice when operation is necessary in gastric ulcer—a formidable operation with a high potential operative mortality except in the best surgical hands; (3) that many of us believe gastric cancer is only seldom engrafted upon gastric ulcer; and (4) that there are available certain criteria which may be applied over a reasonably safe period to permit a definite clinical opinion, the reasons for a reconsideration of the subject become more than academic.

* Received for publication October 31, 1933.
From the gastrointestinal clinic of the Jewish Hospital, Philadelphia.

The liberalizing and humanizing influences of the Renaissance shed the first rays of light upon the cancer problem. For it was not until the sixteenth century that, as a result of the frequent use of the postmortem examination, the nature of cancer of the stomach began to be understood. While the same studies must have revealed many instances of gastric ulcer and gastric cicatrices, Cruveihlier,[2] nearly three centuries later, was the first clearly to distinguish clinically and pathologically between chronic ulcer and carcinoma. It was he, too, who first discussed the question of the transformation of a gastric ulcer into cancer, but he suspected the existence of an additional factor for he stated that "La question de savoir si un ulcère chronique simple peut devenir cancéreux ne me paraît devoir être résolue d'une manière affirmative que pour les individus affectés de la diathèse cancéreuse." *

In the following year, 1840, Rokitansky [3] too recognized the difference between chronic gastric ulcer and cancer, and expressed the opinion that the latter might be implanted upon the former. Since these initial opinions the pendulum has swung back and forth between the two extremes: one that gastric ulcer is a very frequent precursor of gastric malignancy; the other that it is infrequently so. In the beginning, estimates of ulcer-cancer were from about 5 per cent to the 100 per cent of Zenker; then to less than 5 per cent; then to 90 per cent; down to zero; up again to 80 per cent; while in recent years the 5 per cent estimate has once more become popular. Newcomb [4] in the past year has analyzed 102 reports on the subject published between 1848 and 1931. Of these, 51 estimate ulcer-cancer under 10 per cent, 74 less than 20 per cent; and only 15 give an estimate of over 50 per cent. So even an approximate estimate of the frequency of the development of carcinoma on an ulcer basis will be impossible until pathologists determine certain criteria of malignant change.

This problem received its initial airing when Dittrich,[5] in 1848, analyzed 160 cases of gastric carcinoma and found six of these developing in relation to active or healed ulcers. Subsequent reports generally give similar estimates of this complication. Then Steiner and Wollman, in 1866, estimated the incidence as 4 per cent, and Lebert,[6] in 1878, as 9 per cent. The first extreme view was voiced by Zenker [7] in 1882 in a discussion in which he said ". . . dass auch aus dem klinischen Verlaufe vielen, ja der meisten Fälle von Magencarcinom, auf ein vorhergegangenes Magengeschwür zu schliessen sei." † This extreme point of view was reiterated by Mayo Robson [8] (1907), and more recently by MacCarty [9] and his group in this country.

Contrariwise, Duplant,[10] in 1898, attacked such a concept, and detailed eight cases of supposed ulcer-cancer which he considered "en réalité de

* "The question of whether a simple chronic ulcer can become cancerous does not need to be affirmatively answered, it seems to me, except in the cases of those individuals affected by a cancerous diathesis."

† . . . "that from a clinical course many, aye most, cases of gastric carcinoma are superimposed upon a preceding gastric ulcer."

néoplasmes ulcérés." This opinion found support with contemporary and even later workers. Tripier [11] (1898) reported cases in which the primary carcinoma had ulcerated away to such an extent that the true malignant nature of the process was recognizable only from the finding of metastatic lesions. Later Stromeyer,[12] and more recently Moszkowicz,[13] have stressed the frequency of ulceration in primary gastric carcinoma. Stewart,[14] in his excellent studies, reports an incidence of cancers in ulcers surgically removed as 17 in 277, or 6.5 per cent. He aptly notes that the frequency with which well healed scars are encountered in the stomach indicates that the actual percentage of chronic ulcers which become malignant must be much less than this. In a recent, careful study, Dible [15] found that of 126 gastric ulcers considered benign clinically and grossly at operation, all failed to show any evidence of malignancy upon microscopic examination. Further, had even those ulcers considered clinically suspicious of malignancy been included, the result would have been only a 4 per cent ulcer-cancer incidence. Finally, in this country Ewing [16] in his authoritative work on neoplastic disease concluded that cancerous change does not take place in more than 5 per cent of gastric ulcers.

At the present time, the most reliable estimate of this complication can probably best be achieved by tracing the after history of those cases of gastric ulcer that have been treated by gastro-enterostomies. Reports of several such series give very low percentages for the subsequent development of malignancy and may be summarized as in the chart below:

Investigator		Number of Cases	Percentage of cases later showing malignancy	
Kocher	(Series 1)	50	0.0	Follow-up period of 2 to 12 years
Kocher	(Series 2)	30	0.0	
Gressot		No figure	2.3	
Paterson		No figure	1.0	
Belleter		112	0.9	
Greenough and Joslin		164	0.6	
Banberg		1025	2.1	
Sherrin		200	0.0	
Exalto		208	1.0	

Such figures, we believe, speak eloquently against any high incidence of cancer engrafted upon simple gastric ulcer. Bevan [17] has recently given an apt explanation for the incidence of ulcer-cancer. Believing that this occurs in only 2 to 5 per cent of gastric ulcers, he sees no reason why 2 to 5 per cent of peptic ulcers should not develop into malignancy, since 4 to 5 per cent of those who live to 40 to 60 years die of cancer of the stomach.

Granting that a small percentage of gastric ulcers may undergo malignant change, is there any means of detecting such a change clinically, and—a matter of even greater importance—have we any means of clinical differentiation between a benign gastric ulcer and an ulcerating carcinoma—lesions which may simulate each other closely?

Evidence from the History

Historical evidence for or against the possible malignancy of an ulcerated lesion of the stomach may best be considered under the following headings:

1. Duration of symptoms
2. Nature of symptoms
3. Response of symptoms to treatment

Much has been written on the value of historical data in the differentiation between ulcer and cancer. One fact which all writers have noticed, but which in practice is still frequently lost sight of, is the short history generally obtained in gastric carcinoma. It behooves every physician who is consulted by a patient past 30 years of age with a history of digestive symptoms, very carefully to eliminate the possibility of gastric carcinoma—especially in those cases where the history of gastric symptoms is of less than a year's duration and where the previous digestion has been excellent. In chronic gastric ulcer, on the other hand, the history of gastric symptoms is apt to be long. In our 53 cases of gastric cancer, the duration of symptoms varied from 10 weeks to two years, with 92 per cent giving a history of less than one year of symptoms, while a group of 34 ulcer cases gave an average history of 7⅓ years. Similar figures have frequently been published. Cabot and Adie [18] in 116 cases of cancer found that the majority gave a history of less than one year of symptoms and a very considerable percentage gave a history of six months or less. Stewart,[14] in 146 cases of simple ulcer found the average duration of symptoms from the history was 7.5 years, and in 48 cases of primary cancer the average was one year. Dible [15] recently recorded an average historical period in 108 ulcers of 10⅓ years and in 28 cases of cancer an average of 2¼ years. His rather higher average for the cancer series was due to one case which had a duration of 20 years. Such a case as this brings up the question as to how much value can really be placed on previous symptoms and their duration. Of the importance of the short history in pointing toward cancer there can be no doubt, but great caution should be used in interpreting a long history as indicating ulcer or especially, when malignancy is found, as indicating ulcer-cancer. It should be remembered that the history of gastric ulcer is frequently atypical, and that disturbances in other organs, notably the gallbladder, colon, and pancreas, may be responsible for the very same kind of atypical ulcer symptoms. Such a story must not be too readily taken as indicating a gastric ulcer of long duration, should a gastric lesion be found. Even with a typical ulcer history, one must not leap to the conclusion that the gastric cancer found is engrafted upon an ulcer, because that history may have been due to a preëxisting duodenal ulcer, as was shown in one of our cases. Osler [19] in 150 cases of carcinoma found an ulcer history in 2.6 per cent but not in a single case could it be proved; and Cabot and Adie,[18]

applying as criteria of ulcer history that the pain have its site in the upper abdomen and that it occur in some demonstrable relation to the taking of food and continue over a reasonable period of time, found that only nine of their 116 cases could be regarded as having an ulcer history.

Further evidence of the false dependence that may be placed on a long history as indicating a preceding ulcer is well illustrated by another case of Dible's.[15] In this instance the history was of eight years' duration and therefore suggestive of gastric ulcer. The stomach was explored but no lesion was found. Two years later the same patient was reoperated upon and an extensive carcinoma was found. Obviously had this been the first operation, the history could have been considered as indicating ulcer-cancer. Briefly, then, the average primary cancer history is short; that of simple ulcer comparatively long—but a long history is unjustifiable presumptive evidence of ulcer-cancer.

Can the amelioration, or even the disappearance, of symptoms under treatment be taken as evidence of benignity? This question must be answered negatively. Primary gastric carcinoma, especially of the ulcerating type, will frequently show very marked subjective improvement on an ulcer regime. Symptoms may disappear entirely and weight-gain be registered. Such changes may lead to a false security. They are doubtless due to diminution of the associated inflammatory reaction which may also even lead to temporary improvement in the roentgen-ray findings. Considered alone such changes cannot be taken as positive evidence of benignity.

Evidence from Gastric Analysis

In 1879, von den Velden [20] first stated the opinion that in cases of gastric carcinoma the stomach contents never showed any free hydrochloric acid. While more than 40 years have elapsed since Miehe [21] challenged this view, reporting at the time five proved cases of gastric carcinoma which had shown free hydrochloric acid after an Ewald meal, it, nevertheless, still appears to be an accepted belief among many practitioners that the presence of free gastric acidity is against the diagnosis of cancer. This is probably so because the absence of free gastric acid has been so frequently stressed, especially in the early literature. Thus Ewald [22] believed that except in very small early lesions, or in cases of ulcer-cancer, the absence of free acid was practically constant. Boas [23] records anacidity in 77.5 per cent of his cases; Hartman [24] in 53.7 per cent; and Hurst,[25] recently, in 65 per cent of 74 cases, while Bloomfield and Polland [26] found an anacidity in 69 per cent of their cases even after histamine. Of our own series of 53 cases, 36 had had fractional analysis, of whom 16 or 44.4 per cent showed an anacidity; 11 or 30.6 per cent showed a hypochlorhydria; 6 or 16.6 per cent a normal acid response; and 3 or 8.3 per cent hyperchlorhydria.

While sight must not be lost of the fact that anacidity frequently accompanies gastric carcinoma, one must also realize that nearly as many may

show free acid, and that about 25 per cent of the cases show a normal acidity or higher. Furthermore, the number of cases with moderate or normal acidities is far too great to be accounted for by the small ulcer-cancer group. If, moreover, we consider the normal, rising incidence of anacidity with each decade, and the frequency of carcinomas in corresponding periods, some of the incidence of anacidity in gastric cancer may be attributed to coincidence.

Age (years)	Per cent of anacidity in normals (Bloomfield and Polland [26])	Per cent of incidence of cancer (Cabot and Adie [18])
20–29	5.3	3.4
30–39	9.5	11.2
40–49	16.7	15.5
50–59	24.0	36.2
60	35.4	32.7

We feel that anacidity is frequently present in gastric cancer, but that it has been so emphasized in the past that today its absence is often falsely taken to mean the absence of cancer.

Since Zenker first called attention to the persistence of free hydrochloric acid in the stomach contents in ulcer-cancer, it has often been intimated that such a finding in cases of gastric carcinoma points to an ulcer origin. Thus Hurst [25] states that in a large percentage of carcinomas which yield unmistakable pathological evidence of being secondary to a chronic ulcer, free hydrochloric acid is found. Orator [27] records free hydrochloric acid in 12 of 14 ulcer-cancer cases and achlorhydria in seven of eight primary carcinomas, while Stewart,[14] in recording a high normal acid or hyperacidity in six of nine ulcer-cancer cases, states his belief that such curves are the rule in ulcers which have undergone malignant transformation. This latter author also presents as an alternative hypothesis that a small proportion of primary carcinomas arises in stomachs which still possess a normal or hypernormal free acid secretion. Such cases, he believes, would be more likely than those associated with achlorhydria to undergo secondary peptic ulceration. However, because of the short history of a year or less in six of the nine of our normal and hyperacid cases; because of the ulcerating lesion found in so many of our achlorhydric group, plus the fact that the incidence of gastric carcinomas which show adequate free hydrochloric acid is entirely too high to be accounted for by the ulcer-cancer group, we are unable to subscribe to the above views. We should also call attention to the consideration of a concomitant duodenal lesion in some of the cases showing a high acidity. The frequency of duodenal ulcer, especially in men; the high level of gastric secretion, even when the lesion is under control; the likelihood of a long gastrointestinal history as previously pointed out in such cases—all these should be kept in mind. One of our hyper-acid cancer cases which came to postmortem examination showed in addition the presence of an apparently healed duodenal ulcer.

Of the numerous theories suggested to explain the relatively high incidence of anacidity in gastric cancer, that of an associated chronic gastritis appears most logical and receives the greatest support. Lebert,[6] who was the first thoroughly to study this phase of the problem, found such a gastritis at a remote distance from the growth in 41 of 56 cases. Similar findings have been repeatedly recorded. Hurst [25] recently stressed this association and considers chronic gastritis as the most common predisposing condition responsible for gastric malignancy.

In 1929 Hurst [25] stated, and he recently reiterated in the Alvarez Lecture delivered in Washington, May 8, 1933, before the American Gastro-Enterological Association, that he has never seen a case of gastric carcinoma in which free hydrochloric acid was present at an early stage and disappeared as the disease advanced. One of us (H. S.) has recently observed just such a change in a patient (E. M.) who refused operation at the beginning of her illness. Hurst [25] records three cases of gastric ulcer in which a test meal had been given before and after the onset of malignant degeneration. The hyperchlorhydria which was present in two, and the normal acidity in the third, were maintained undiminished after malignant degeneration had occurred.

Briefly, we believe that, given an ulcerating gastric lesion, an accompanying anacidity is presumptive evidence in favor of carcinoma as against benignity; but the presence of normal acidity or of hyperacidity is of little, if any, value in militating against malignancy.

Value of Blood Reaction in Gastric Contents

The older literature has frequently suggested that the finding of a constant occult blood reaction in the stool on repeated examination speaks in favor of malignancy, as against the intermittent occult blood found with benign ulcer. We do not believe that the stool reaction can be of much help unless it becomes negative and remains so. A positive test cannot be taken seriously because the benzidine reaction, which is extremely sensitive, may in many cases be found repeatedly positive because of very slight amounts of blood in the stool derived from the region of the anal canal, or even because of other catalysts in the stool.

Of considerable value, however, is the reaction for blood in the gastric contents when found on repetition of the fractional gastric analysis. In benign ulcer, if occult blood is present at the time of the first aspiration, the reaction rapidly becomes negative under a proper medical regime. In malignant ulceration the reaction continues to be positive even in spite of the presence of marked subjective improvement, or objective improvement, as evidenced by weight-gain and a decreased niche in the roentgenograms.

Roentgen-Ray

The roentgen-ray, so potent an agent in detecting an organic gastric lesion, is, unfortunately, of little help in our present problem because the

roentgenologist is unable to differentiate between an ulcer defect due to a benign lesion and one caused by an ulcerating carcinoma. Both may produce identical roentgen signs. The size of the lesion is not a reliable differentiating sign, and even a decrease in the size of the niche under treatment is not certain evidence of benignity, because such a change may be due, as in the case of symptomatic improvement, to diminution of the associated inflammatory reaction.

The location of the lesion has, however, received considerable attention, both as to the location of primary gastric malignancy and the ulcer lesions which undergo secondary carcinomatous change. Thus Cabot and Adie [18] state that in general 60 per cent of cancers occur at the pylorus, while about 12 per cent of ulcers occur in the same area; the distribution on the lesser curvature is just the reverse, and Stewart [14] states that fully 80 per cent of chronic gastric ulcers occur on the lesser curvature region with most of the remainder at or near the pylorus. Carcinomas, on the other hand, commence in the pyloric region in about two-thirds of the cases. Thus the site of ulcer-cancer in distribution is that of simple ulcer (Stewart [14]: 71 per cent of 17 cases were on the lesser curvature and 29 per cent were pyloric). However, the prepyloric ulcer shows the greatest tendency to malignant change, since Hurst [25] found that no less than three of nine ulcers in the pyloric region showed malignant change as compared with only eight of 172 ulcers on the lesser curvature. Orator,[27] in 334 resections for ulcer, found 11 of 34 in the prepyloric region to show malignant change as compared with six of 300 from the lesser curvature region. This predominance of malignant change in the prepyloric region Hurst [25] attributed to the amount of friction to which this area is subjected.

Briefly, we may state that, presented with an ulcerating gastric lesion, our procedure is as follows:

1. In a case giving a short history of gastric symptoms (especially if the history is less than one year in duration and particularly if perfect digestion had previously been the rule), accompanied by anacidity and the presence of occult or gross blood throughout a fractional analysis, with a lesion close to the pylorus, *immediate surgery* is advisable, but if any of the factors mentioned are absent, a short rigid ulcer regime of not more than three weeks may be tried.

2. If, on the other hand, the history is long, gastric free acidity is maintained, the occult blood reaction positive or negative, and the lesion situated higher on the lesser curvature, the patient is entitled to a *trial medical regime*, since we know that medical cure is effective in benign gastric ulcer.

3. The *criteria for continuation of medical treatment* are as follows: rapid subjective relief; continuous diminution in size of the niche by roentgen-ray; no drop in gastric acidity; and the disappearance of the occult blood reaction in the test meal.

4. If such changes do not occur within six weeks of treatment, roentgen-ray and gastric analysis having been repeated at three-week intervals, then

surgery should be employed. Of the criteria mentioned, we place the greatest stress upon the disappearance of the occult blood reaction in the gastric contents since, as we have pointed out, the other improvements may occur with a malignant as well as with a benign ulcer.

In this connection we wish to place on record the case of E. M., to which we have previously referred, which illustrates the diminution and ultimate disappearance of free hydrochloric acid during the progress of a carcinomatous ulcer.

Case History

Mrs. E. M., aged 56, had a negative gastrointestinal history, except for constipation, for many years. Her present illness started in April 1931, five weeks before this history was taken. At that time she had developed gripping pain in the epigastrium which usually appeared about two hours after meals and lasted a half hour to an hour, after which it was relieved spontaneously. Since the onset, she had developed loss of appetite, sour taste, some belching, and occasional attacks of nausea during pain; she had vomited only three times and these in the last two weeks; no blood or bile was present in the vomitus. There was a loss of six pounds of weight since the onset. Aside from frequent headaches and a feeling of weakness, no other symptoms were noted. Physical examination revealed nothing of note; no mass was palpable in the upper abdomen.

Fractional gastric analysis, May 29, 1931:

	Fasting Residuum	Minutes							
		15	30	45	60	75	90	105	120
Free HCl	35	12	12	30	45	40	30	25	25
Total Acid	47	17	25	50	60	60	45	40	40
Occult Blood	+ 4	+ 4	+ 2	+ 2	+ 4	+ 4	+ 2	+ 2	+ 2

The blood Wassermann was negative. The blood count showed a secondary anemia with 60 per cent hemoglobin and 3,640,000 red blood cells. Weight 124 pounds. On June 3, 1931 roentgen-ray showed a gastric ulcerating lesion involving the posterior wall and the lesser curvature of the antrum toward the pyloric end, perforated, with accessory pocket formation.

The very short history without any previous gastric symptoms, the rather marked occult blood reaction throughout digestion, and the location of the lesion nearer the pyloric end of the antrum made us advise surgery in spite of the normal acid response. The patient, however, refused operation and a strict Sippy regime with rest in bed was instituted. After three weeks the patient showed complete symptomatic relief except for occasional discomfort if she failed to take her alkaline powder. Weight 128 pounds; gain four pounds. On June 20, 1931, the hemoglobin was 61 per cent and fractional gastric analysis showed virtually the same findings as in the first test. On June 22, roentgen-ray showed definite improvement, the lesion appearing to be definitely smaller than the original.

The patient was lost sight of for about two months when she returned giving a history of freedom from symptoms, feeling much stronger and weighing 134¼ pounds, a gain of 10¼ pounds in three months. The hemoglobin was 75 per cent. However, fractional gastric analysis on August 26, 1931 showed that the fasting residuum contained considerable microscopic food not present previously; there was a marked drop in acidity and occult blood was still present throughout.

Fractional gastric analysis, August 26, 1931:

	Fasting Residuum	Minutes							
		15	30	45	60	75	90	105	120
Free HCl	0	0	0	0	0	0	0	5	7
Total Acid	15	10	10	10	10	12	15	15	20
Occult Blood	+3	+3	+1	+1	+1	+4	+4	+3	+2

At the last extraction 280 c.c. were recovered from the stomach, containing 35 c.c. of food. At the previous examination there had been no evidence of motor delay On August 29, 1931 roentgen-ray showed a definite increase in the amount of deformity as compared with the last examination. With the roentgen-ray and gastric analysis findings we were convinced that we were dealing with a malignant lesion, but it was impossible to convince the patient to permit surgery since she was apparently improving. This course continued until her weight reached 135½ pounds.

Fractional gastric analysis, September 11, 1931:

	Fasting Residuum	Minutes							
		15	30	45	60	75	90	105	120
Free HCl	0	0	0	0	7	10	10	10	12
Total Acid	22	15	7	12	17	17	27	22	27
Occult Blood	+4	+2	+1	+1	+1	+1	+2	+2	+1

Fasting residuum showed microscopic food as before and the final extraction was of 115 c.c. containing 30 c.c. of food.

Fractional gastric analysis, December 4, 1931:

	Fasting Residuum	Minutes							
		15	30	45	60	75	90	105	120
Free HCl	0	0	0	0	0	0	0	0	0
Total Acid	10	7	10	5	7	7	10	10	7
Occult Blood	+4	+4	+1	+1	+4	+4	+4	+4	+4

Between the last two analyses there was a return of symptoms, and vomiting became frequent. Weight gradually dropped from 135½ pounds in September to 125¼ in December when she finally consented to operation. On laparotomy an ulcerating carcinoma in the lower segment of the antrum was found.

For contrast let us consider the history of the following patient.

Case History

L. R., male, aged 64 years, denied any gastrointestinal symptoms until three months before the present history was obtained in October 1929. His illness started with a burning pain under the xiphoid which became practically constant. After about a month epigastric pains appeared, usually from 15 to 25 minutes after meals, but at times not until an hour to an hour and a half after meals. He did not know whether food relieved the pain. He never had any night pain. In addition, he had occasional belching and nausea but no vomiting and had lost about 25 pounds since the onset of

his illness. Bowel function was normal. Physical examination revealed nothing of importance.

The pertinent laboratory findings were a hypochlorhydric curve and a positive occult blood reaction throughout the fractional analysis, the blood test being strongest in the latter half of the analysis. The stool was positive, plus two, for occult blood. Blood sedimentation rate was normal. On November 10, 1929, roentgen-ray showed a large penetrating gastric ulcer on the posterior wall and lesser curvature just proximal to the incisive angle.

The age of the patient, the short history of gastrointestinal symptoms, the hypochlorhydria with occult blood present throughout the test meal, the positive occult blood reaction in the stool and the large crater seen by roentgen-ray certainly justified the suspicion of a malignant ulcer. However, with the standards advocated above in mind, the patient was put on a strict ulcer regime. On December 1, 1929, three weeks after starting treatment, a fractional analysis yielded approximately the same type of acid curve, but showed a complete absence of occult blood. The stool, however, still gave a plus one occult blood reaction with benzidine. On December 2, 1929, roentgen-ray showed the niche still present but about half the size noted at the previous examination. In the meantime, clinically there had been complete disappearance of symptoms and the patient had gained one and a half pounds. Treatment was continued and on January 2, 1930, a fractional analysis yielded essentially the same picture as that of December 1, and on the following day roentgen-ray showed total disappearance of the niche. Clinically the patient was entirely free of symptoms and now showed a weight gain of 13 pounds. Three months later this patient was again studied and revealed no evidence of a return of the ulcer, and when last seen, three years after the onset of the symptoms, he was apparently in perfect health.

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FELTY'S SYNDROME

REPORT OF A CASE WITH COMPLETE POSTMORTEM FINDINGS *

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In 1924, Felty [1] reported five cases of an unusual syndrome occurring in undernourished, middle-aged people and characterized by three important clinical features: enlargement of the spleen, leukopenia and arthritis. Recently a sixth case, showing all of the above characteristics and in addition a gastric achlorhydria, was reported by Hanrahan and Miller.[2] In the latter case, a splenectomy was done, this resulting in definite improvement in the arthritis.

We have recently observed a patient who presented all of the above clinical features and whom we therefore believe can be justly classified under this new syndrome. Splenectomy was agreed upon in this case also, but a fatal pericarditis unfortunately precluded the fulfillment of this procedure. Permission for a complete autopsy was obtained, the results of which are included below. We believe that this constitutes the first case report of Felty's syndrome with complete pathologic data.

Case Report

B. T., male, aged 57, American, drill press operator.

Present Illness: Started three years ago when the patient first experienced pain and swelling of both shoulder joints. This later assumed a migratory character with successive involvement of almost all of his joints. In about one year the knees and ankles became involved, making walking at times impossible. The pain and swelling about the joints were the most prominent features but occasionally they would appear red and inflamed. A loss of 20 pounds of weight occurred during the year. At this time he visited Hot Springs, Arkansas, where under a regime of baths and physiotherapy he had a complete remission of his arthritic symptoms. Since that time, except for an occasional twinge of pain in his joints, the patient has suffered no disability until six weeks ago when pain in the back and right shoulder returned with its former severity. There was some swelling and slight redness, followed by involvement of the elbows, fingers, knees and ankle joints.

Past History: Patient had the usual childhood diseases. In 1914 his right eye was removed following a burn. In 1919 a gastro-enterostomy and appendectomy were performed for peptic ulcer and chronic appendicitis respectively. In the same year all teeth (abscessed) were removed. There was no history of sore throats and no symptoms referable to the heart and lungs. Both syphilis and gonorrhea were denied. The family and marital history were negative.

Physical Examination: The patient was a middle-aged, poorly-nourished, white male with a sallow, sub-icteroid color to the skin. Eyes: right missing; left normal. Nose: negative. Mouth: teeth removed. Tonsils: atrophic. Heart: rate 100, regular. Left border 10 cm. to left of the midsternal line in the fifth intercostal space; right border substernal. Heart sounds: fair quality, no murmurs. Blood pressure:

* Received for publication February 7, 1934.
From the Department of Internal Medicine, Harper Hospital, Detroit, Michigan.

100 systolic and 75 diastolic. Vessels: moderately sclerotic. Lungs: negative. Abdomen: flat, well healed surgical scar from xiphoid to below umbilicus. No tenderness. Spleen: felt three fingers' breadth below the costal margin. Surface smooth and firm with notch palpable. Liver and kidneys: not felt. Genitalia: normal. Prostate: slightly adenomatous but not tender or boggy. Extremities: swelling and deformity about elbows, shoulders, knees and interphalangeal joints with interosseous atrophy. There was marked limitation of function and motion.

LABORATORY DATA

Blood Examinations

Date	Hb. %	Retic. %	R.B.C.	W.B.C.	P.	L.	M.	E.	Morphology
2/2/33	57		4,070,000	3,100	68	30	2		
2/4/33				3,350	41	44	5	7	3 Myelo.
2/11/33	52		3,700,000	3,450	44	47	4	3	2 Myelo. Moderate achromia and anisocytosis.
2/14/33	62	15	3,030,000						
2/15/33				4,800	66	31	0	3	
2/18/33				3,700	71	23	2	4	
2/23/33	48		3,430,000	6,400	62	32	3	3	
3/3/33	48		3,420,000	4,400	60	34	0	6	
3/10/33	36		3,490,000	5,300	69	22	2	7	

Schilling Hemogram: (2/14/33)—W.B.C. 3,000 Poly. segm. 24% } 50% Lymphocytes 43%
" juv. 6% } Monocytes 3%
" stab. 20% } Eosinophiles 3%
Basophiles 1%

There was a moderate erythrocytopenia with some polychromasia. The leukopenia was associated with a neutropenia. Left shift of marked degenerative type. Nuclei showed toxic changes. There was a relative lymphocytosis and reticulocytosis.

Blood Fragility: normal. *Bleeding Time:* one minute. *Clotting Time:* two and one-quarter minutes. *Blood Platelets:* 550,000.

Urinalysis: Repeated examinations showed a urine of high specific gravity varying from 1.018 to 1.028. Occasional traces of both sugar and albumin. Sediment negative. *Phenolsulphonephthalein Test:* Intravenous—60% return of dye in two hours.

Gastric Analysis: No free hydrochloric acid with Ewald test meal. Results the same after histamine. No lactic acid or occult blood. Microscopical examination revealed a few W.B.C. and epithelial cells, and numerous flagellates. (Giardia lamblia). *Basal Metabolism:* Plus 28. (Approx. weight and height used in calculation).

Blood Chemical Tests: N.P.N., 31.5 mg.; *Calcium*, 9.6 mg.; *Phosphorus*, 3.3. mg.

Glucose Tolerance: Blood sugar increased progressively from 105 to 234 mg. after 2½ hours following the ingestion of 100 gm. glucose. Tolerance decreased.

Icteric Index: 2. Van den Bergh test: negative, both direct and indirect.

Liver Function Tests:

Lactose Tolerance		Bromsulphthalein Dye %
Fasting Sugar	0.090%	
1 minute	0.125	60
2 "	0.143	60
3 "	0.133	40
5 "	0.117	30
10 "	0.117	5
15 "	0.100	0

Liver function normal.

Blood Cultures: (2): No growth. *Widal:* (Typhoid and Para-typhoid A and B): negative. *Agglutination for Melitensis* (Huddleson): negative. *Kahn Test:* negative.

Roentgenological Reports: A single film of the chest with the portable unit revealed the diaphragm leaves to be normal in height and contour, without evidence of fluid in either pleural cavity. The heart, aortic and tracheal shadows were normal in appearance. There was some accentuation of the trunk markings with slight impairment in the radiability of the middle and lower lobes on the right side, but no frank parenchymal infiltration or pulmonary consolidation. The bony thorax was intact.

A film of both hands and wrists in the dorso-palmar projection showed moderate soft tissue swelling about some of the phalangeal joints, but no destruction of the cartilage and no bone absorption. There was a slight tendency to over-growth of the articular margins of some of the phalangeal joints, with slight hypertrophy of the cortical portion of the shaft of the second metacarpal on the right side. (Figure 1.)

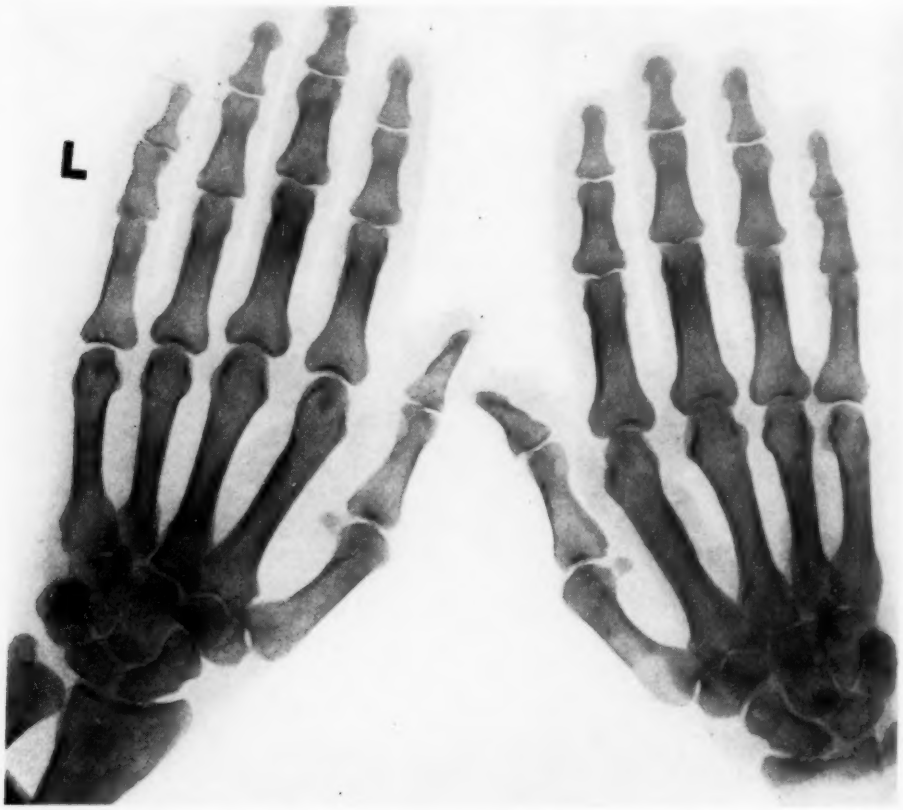

FIG. 1. Roentgenograms of hands.

Electrocardiographic Report: Voltage low. Regular sinus rhythm. P–R .16″. Q–R–S .08″ T_1 upright. T_2 upright. T_3 flattened and slightly diphasic. S–T_1 and S–T_2 distinctly elevated. S–T_3 normal. *Conclusions:* Myocardial damage due either to pericardial effusion, pericardial adhesions or coronary thrombosis.

Clinical Course: From the time of his admission to the hospital, the patient was partially disabled by his arthritis, but was at no time considered acutely ill. Throughout most of his course, the temperature was irregular, varying between 99° and 101°. Because of the fever, accompanied by persistent leukopenia, agglutination tests for typhoid, paratyphoid and malta fever were performed. All were negative. The pig-

mentation of the skin (noted in all of Felty's cases) was studied by means of the icteric index and Van den Bergh reactions, but these were likewise negative.

For the first two weeks of his hospitalization, the course remained relatively uneventful. On February 15 he complained of pain in the right chest, this being accompanied by signs of fibrinous pleuritis. Two weeks later a pericardial friction rub was heard for a period of several days. It recurred 10 days later without associated pain or temperature elevation. That night, just preceding the day set for a splenectomy, the patient expired unexpectedly.

Necropsy

The body was that of an emaciated, white male, with moderate postmortem hypostasis. The muscles of all extremities were atrophic, with apparent enlargement of the joints. The right eye was missing.

Fig. 2. Heart muscle showing areas of perivascular round cell infiltration extending along connective tissue septa deep into myocardium. These areas are continuous with the pericardial exudate. (× 80.)

Brain: Normal to gross inspection. The dura was normally adherent to the skull. *Pituitary:* Weight, 0.545 gm. Normal appearance; microscopically there was a pronounced basophilia. *Spinal Cord:* grossly normal; microscopically no significant pathological findings. *Thyroid:* Adenoma. *Parathyroid:* No gross or microscopic findings. *Lungs:* Both lungs were firmly adherent to the parietal pleura by dense, fibrinous adhesions. There was marked congestion of both lungs with multiple scars, especially in the upper portions; microscopically there was moderate emphysema and

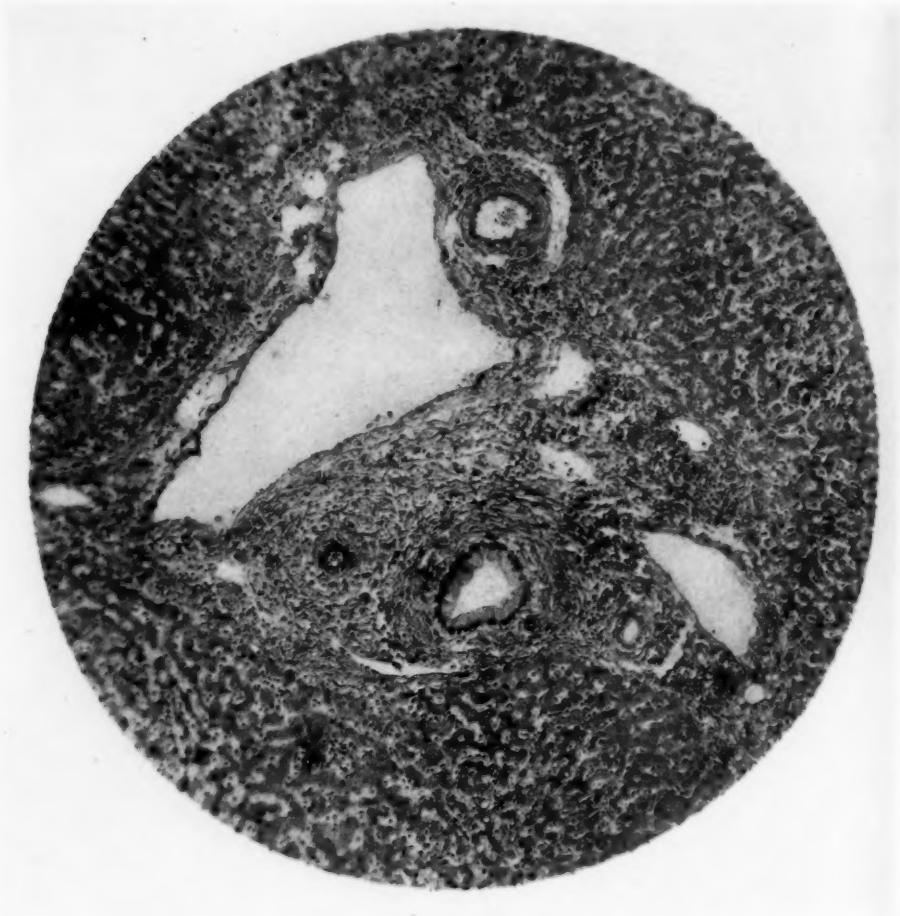

FIG. 3. Liver showing round cell infiltration of Glisson's islands.

edema with numerous heart failure cells. Healed and caseating tubercles were scattered throughout. *Heart:* The surface of the heart was covered with a dense, heavy, fibrinous exudate binding it firmly to the pericardium. It was slightly enlarged to the left, and on section displayed a left ventricular wall of normal thickness and appearance. The right ventricular musculature was almost completely replaced by fatty infiltration. The auricular muscle and all valves appeared normal. The coronary arteries were grossly negative. Microscopically the pericardium showed an acute septic fibrinoplastic pericarditis with extension along the fibrous tissue septa deep

into the heart muscle. These areas contained lymphocytes, many plasma cells, eosinophiles and young connective tissue cells. Only an occasional polymorphonuclear cell was seen. (Figure 2.) There was moderate hypertrophy of the ventricular muscle with myxomatous degeneration of the connective tissue of the auricular wall. The aortic adventitia showed an acute, septic inflammation with marked edema and necrosis. *Stomach and intestines:* These viscera were markedly dilated with gas. A well functioning posterior gastroenterostomy connected the stomach with the jejunum.

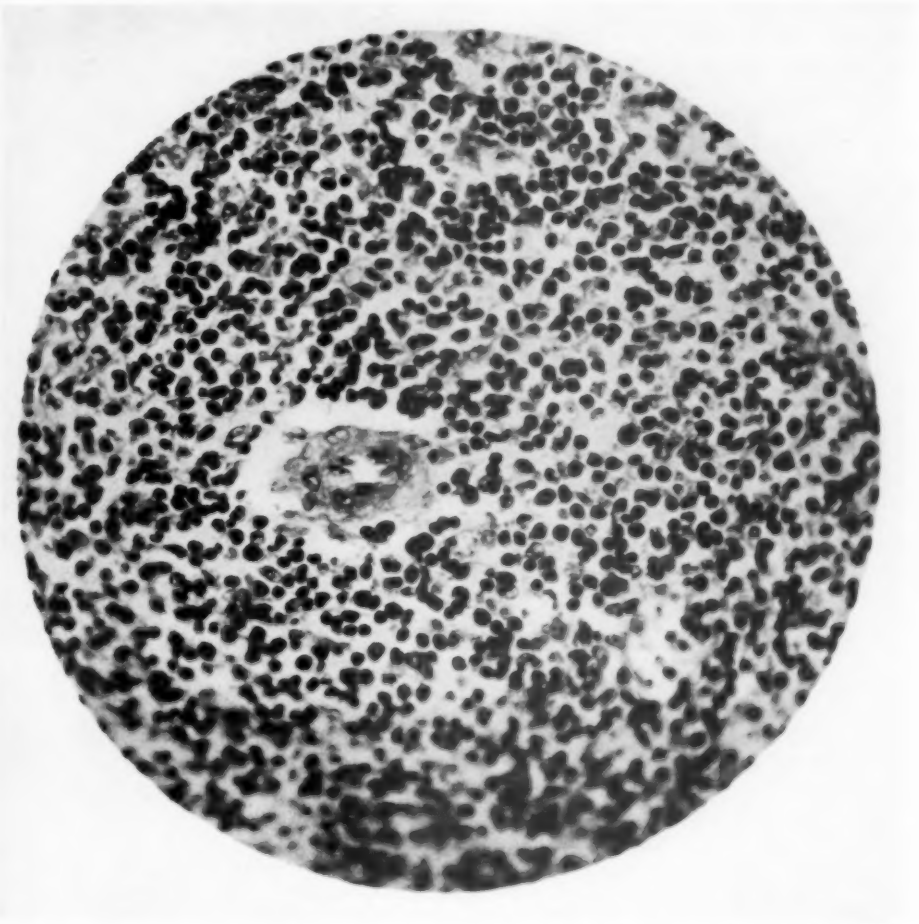

FIG. 4. High power view of spleen showing active myelosis of splenic sinuses. (× 320.)

Liver: very much enlarged, the lower right border extending down to the crest of the right ilium. Weight, 2100 gm. On section there was moderate congestion, with round cell infiltration of Glisson's islands, and regeneration of liver cells as from toxic injury. (Figure 3.) *Spleen:* enlarged, weighing 510 gm. On section it was soft in consistency; microscopically there was diffuse fibrosis with dilatation of the splenic sinuses. The latter showed areas of myeloid activity with numerous plasma cells and eosinophiles, and an occasional bone marrow giant cell. There was diffuse, chronic septic splenitis. Large cavernous hemangioma, approximately 3 mm. in

diameter. (Figure 4.) *Kidneys:* appeared normal grossly and on section. The capsule stripped readily; microscopically there were localized areas of round cell infiltration; otherwise normal. *Adrenals:* left, 7.5 gm.; right, 9.5 gm. Marked lipoidosis of cortex. Medulla normal in appearance. *Bladder:* wall of normal thickness and appearance. *Prostate:* moderately large adenoma; microscopically there was some round cell infiltration of the prostatic portion of the urethra and also throughout the capsular and peripheral prostatic tissue. *Pancreas:* normal size and consistency. No important microscopic findings. *Knee joint:* (removed in its entirety). (See figures 5 and 6.) Microscopically there was very active chronic inflammation of the

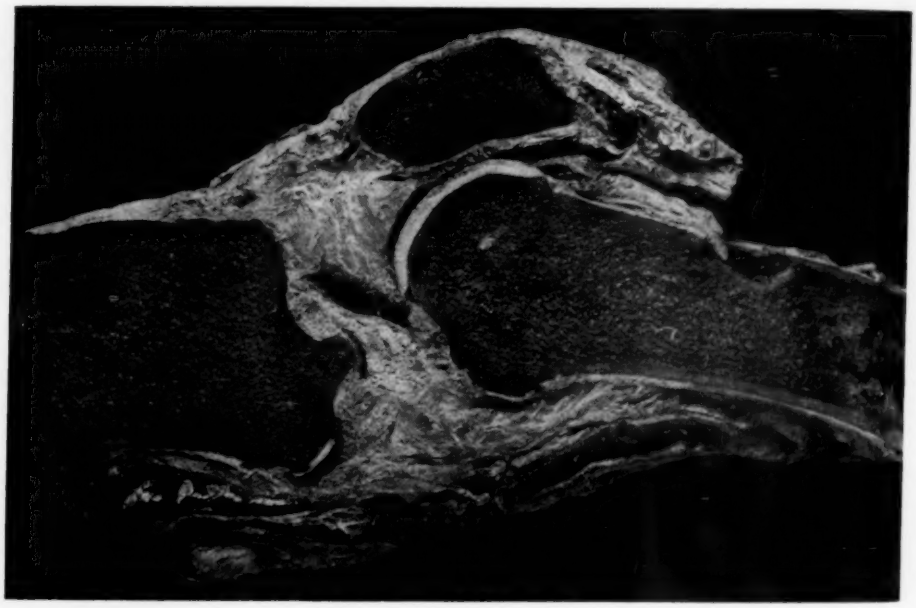

FIG. 5. Sagittal section of knee joint.

periarticular tissue; and intense round cell infiltration of the periosteum in the neighborhood of the joint. The infiltration consisted of lymphocytes and plasma cells, accompanied by a marked connective tissue proliferation. The synovial membrane showed the same picture as the above. *Bone marrow:* (Sternum), hyperplasia of marrow for patient's age with few bone marrow giant cells. Active myelosis throughout. *Bone:* general eccentric atrophy of bone with widening of marrow space and thinning of trabeculae. *Lymph node:* (hemolymphnode) myeloid changes with moderate edema and deposits of hemosiderin. *Sympathetic ganglia:* no microscopic changes of note.

DISCUSSION

In his original article, Felty[1] concluded that the syndrome described by him was best explained on the basis of a single pathologic process, rather than upon the existence of two or more distinct clinical entities occurring coincidentally in the same individual. The pathologic data presented in the case herein reported substantiate the former view. We are further of the opinion that this pathological process is of a chronic infectious nature.

FIG. 6. Photomicrograph of knee joint showing round cell infiltration of periosteum and synovial membrane. (× 80.)

The splenomegaly characteristic of Felty's syndrome has already been described in connection with long standing infectious processes. Thus Giffin noted its occurrence in association with furunculosis, arthritis, endocarditis, colitis, etc., and to it gave the name of "chronic infectious splenomegaly."[3] The clinical picture in each case closely simulated that found in splenic anemia—an analogy brought out by Felty in his cases. In a separate article, Giffin[4] reported one case and reviewed one from the literature (Stillman) in which the splenomegaly was associated with a persistent eosinophilia, both of the peripheral blood and hemopoietic organs (spleen, marrow, lymph glands) as well. The eosinophilia was attributed to the long standing infectious process responsible for the splenomegaly.

More recently, Ward[5] described a similar group of pathologic entities to which he gave the name "chronic septic splenomegalies." In these cases

also, there was noted a variety of etiologic factors but in all, the underlying lesions were similar. The latter were especially manifest in the lymphadenoid tissues of the body with enlargement of the spleen and, in some cases, of the liver and lymph glands as well. Histologically there was evidence of chronic inflammation, i.e., fibroblastic or plasma cell reaction, with no other specific features. It is our belief that the splenomegaly of Felty's syndrome, characterized histologically by chronic splenitis, fibrosis and eosinophilia as noted in our case, belongs to this same group of splenic diseases described by Giffin and by Ward.

The blood picture representing the second characteristic of the new "syndrome" is likewise consistent with the theory of a chronic infection. The secondary anemia, noted in all cases reported, is a common accompaniment of long standing infectious processes. Its association with chronic arthritis has long been recognized.[6] The leukocyte count, while usually slightly increased in arthritis,[6] has been found reduced in some instances. Thus Eaton [7] in a study of 250 cases, found a leukopenia in 22 per cent. Similarly, in their discussion of Still's disease, Weissenbach and François [8] point out the variability noted in the leukocytic picture of this syndrome, the initial leukocytosis and polynucleosis frequently giving way later to a leukopenia and lymphocytosis. Likewise, Ward [5] in his group of chronic septic splenomegalies described a leukopenia and low grade eosinophilia, in the chronic stages of the disease process described by him. The left shift of the polymorphonuclear cells noted in the Schilling hemogram of our case is further evidence for the infectious nature of this blood picture.

The association of splenomegaly and leukopenia with other chronic infections has been frequently noted. Thus Osler [9] described a case of syphilitic arthritis with an enlarged spleen and leukopenia. At the present writing, one of us (A. E. P.) has under observation a case of mycotic infection of the lung associated with arthritis, an enlarged spleen and leukopenia. Cases of primary tuberculosis of the spleen have likewise been reported in which there was a definite leukopenia.[10, 11]

The arthritic manifestations of Felty's syndrome, characterized clinically by their chronicity and at the same time by the relative benignity of the objective features, were present in our case. While there was some swelling of the involved joints with moderate interosseous atrophy and limitation of motion, there was no roentgenological evidence of bone absorption or destruction. (Figure 1.) Histologically, the joint (knee) was not unusual. The active inflammatory process involving the periarticular tissue and synovial membrane is characteristic of that produced by a chronic infectious process.

Summary

In the above discussion we have attempted to show that the underlying pathologic process believed by Felty to exist in this symptom complex, is not new or distinctive, but probably one which results from a chronic infection.

Conclusions

A case with autopsy is presented which has all the clinical features of the syndrome described by Felty in 1926.

The pathologic findings of the case here presented seem to indicate a chronic infectious process.

The symptom complex of arthritis, splenomegaly and leukopenia is probably not a new disease entity.

Note. Photographs were made by Frank N. Ruslander of Harper Hospital.

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TUBERCULOMA OF THE SPINAL CORD*

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Tuberculoma of the spinal cord may develop within the substance of the cord itself (the intramedullary form), or within the spinal canal external to the cord (the extramedullary form). The following report is of a case of intramedullary tuberculoma. Such instances are of infrequent occurrence. The case reported is the only one observed in the 5,344 tuberculous patients in our records. Kernohan, Woltman and Adson [1] in a group of 51 cases of intramedullary cord tumors found only one case of tuberculoma. In 1922 Thalhimer reviewed the literature and collected 52 reported cases of intramedullary tuberculoma of the spinal cord; with Hassin [2] he reported an additional case. From papers published since Thalhimer's review I have collected five additional cases, described by Dandy,[3] Anderson,[4] (two cases) Waring [5] and Kernohan, Woltman and Adson.[1] To these may be added the following case:

Case Report

C. K., a white married female of 27 years, was born in 1902. In childhood she had measles, mumps, chicken pox, rather frequent "colds" and "rheumatism." At the age of 10 she had an attack of pleurisy. At the age of 18 she had a submucous resection performed. She was married at 22. When she was 25 her appendix was removed.

In 1929, when the patient was 26 years of age, she began to feel "run down" and lost four or five pounds in weight. Though she improved again in health for a while, in the first two months of 1930 she again began to lose weight, had frequent "colds" and developed hoarseness. In April of 1930 she had a pulmonary hemorrhage of 15 to 20 c.c. In June, cough and expectoration, hoarseness, night sweats and diarrhea were noted. The sputum was then found to contain tubercle bacilli.

On admission to the Glen Lake Sanatorium on October 22, 1930 examination disclosed far advanced pulmonary tuberculosis, laryngeal tuberculosis, and perirectal (fistula) tuberculosis. The prognosis was apparently a hopeless one.

On February 3, 1931 it was noted that the patient was weaker than on admission, having run constant fever and tachycardia. She complained of some soreness of the throat and of slight pain on deglutition.

On February 13, 1931, the note was made that she complained of some pain in the left sacro-iliac region which radiated down the lateral aspect of the left thigh. This was not intense but she found it difficult to get in a comfortable position. She complained of some difficulty in motion and of a feeling of numbness in the whole extremity, yet she responded when tested with pain and tactile stimuli. The patellar and Babinski reflexes gave normal reactions. The right lower extremity was found normal. A week later, on February 20, the pain, weakness and numbness of the left lower extremity were still present.

On March 19, 1931, a note was made that obstinate constipation had been present for two weeks, though prior to that time the bowels had acted very normally.

A neurological consultant, Dr. R. S. Ahrens, examined the patient on April 8, 1931. The cranial nerves were found normal. The biceps reflexes were equal and

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normal. The knee jerks and ankle jerks were equal and exaggerated, plus 3. Babinski's reflex and Oppenheim's sign were positive on both sides. The abdominal reflexes were decreased on the left and not obtained on the right. Deep sensation, including vibratory sense, was markedly impaired over both lower extremities. Motility of both extremities was impaired but the weakness and loss of control were greater on the left. Superficial sensation was disturbed over both lower extremities corresponding to the level of the fourth or fifth lumbar segment. The presence of a spinal cord tumor was suspected.

On April 20, 1931, frequency of urination was noted. (The later findings of renal and vesical lesions probably explain this symptom).

On May 31 the right lower extremity had become involved as completely as the left; and control of the anal and vesical sphincters had been lost. The patient died on June 9, 1931.

Roentgen-Ray Reports. October 27, 1930: bilateral parenchymal tuberculosis of both upper lobes with bilateral cavitation. February 2, 1931: extension of the lesions in both lungs. March 20, 1931: lumbar spine normal.

Urine Examinations. The routine urine examinations were essentially negative aside from a trace of albumin, occasional white blood cells and the presence of granular and hyaline casts in a few specimens. A guinea pig was injected with urine weekly (4/30/31 to 5/28/31). The pig died of tuberculosis on 6/1/31.

Blood Examinations.

10/24/30: R.B.C. 4,250,000; HB. 72 Sahli; W.B.C. 9,450.
4/9/31: R.B.C. 3,740,000; HB. 58 Sahli; W.B.C. 12,200.

The differential counts were normal. The Kolmer reaction was negative.

Sputum. Each monthly examination of the sputum showed tubercle bacilli.

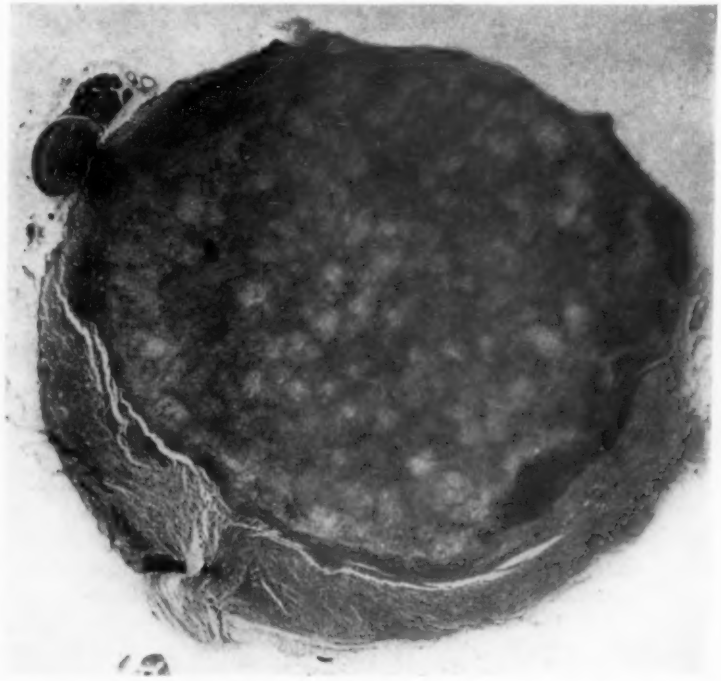

FIG. 1. Cross section of spinal cord showing intramedullary tuberculoma.

Autopsy

(C. C. Van Winkle, M.D.) Summary of essential data.

Pleural Cavities. There were dense adhesions over the left apex and less dense adhesions over the right. The tracheal nodes were large and firm and contained tubercles.

Lungs. In the right lung a small cavity was found in the lateral part of the upper lobe. There were tubercles scattered throughout the whole lung. The upper

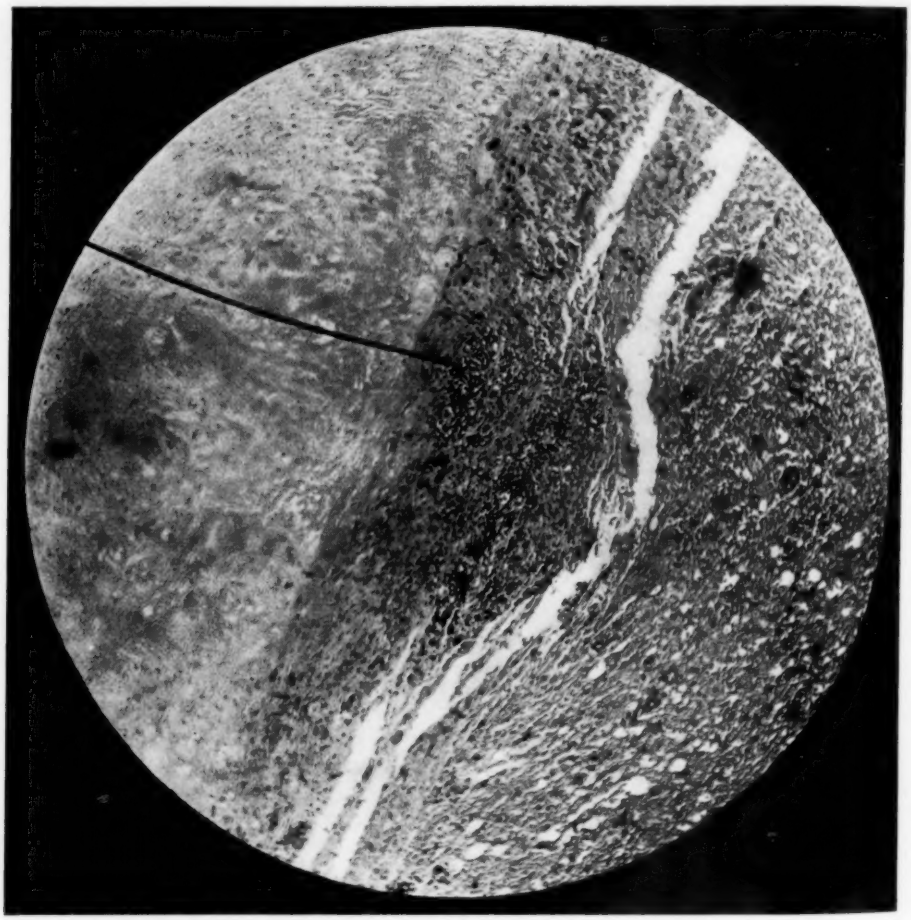

Fig. 2. Microscopic section of margin of tuberculoma. The location of a giant cell is indicated by the pointer.

lobe of the left lung showed a large multilocular cavity; and there were two smaller cavities in the lower lobe. Tubercles were numerous throughout the remainder of the lung.

Intestines. There were extensive ulcerations below a point 35 cm. from the pylorus. Most of the ulcers showed tubercles on the peritoneal surface. There was a perirectal fistula opening 1 cm. to the left of the anus, but its internal connection

with the rectum could not be discovered. The mesenteric glands were enlarged and firm and contained tubercles.

Kidneys. The left showed tubercles between the cortex and medulla and the right showed some tubercles in the cortex. The inner surface of the bladder was covered with a granular purulent material; and there was an area of marked congestion around the urethral orifice. No tubercles were seen.

Spine. The bodies of the ninth, tenth, eleventh, and twelfth dorsal and first lumbar vertebrae were removed with a corresponding section of the cord. The vertebrae and the meninges were found entirely normal. The cord did not appear enlarged but on section at the level of the fourth lumbar segment it was found to contain a tumor. The growth was elliptical in shape and measured 2.0 by 0.9 cm. It appeared to be entirely intramedullary and had replaced almost all of the cord tissue. (Figure 1.)

Microscopic Examination. Sections of the tuberculoma in the cord demonstrated its tuberculous nature and showed the presence of giant cells (figure 2). Tubercle bacilli were demonstrated in sections of the cord.

In addition, the microscopic examination showed the presence of tuberculous lesions in the lungs, spleen, liver, small and large intestines, right and left adrenals, kidneys, Fallopian tubes, mesenteric and tracheal lymph nodes. Tubercle bacilli were demonstrated in the tissues of the lungs, liver, intestines, Fallopian tubes and lymph nodes.

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THE VALUE OF A NEUTRALIZATION TEST OF GASTRIC ACIDITY IN PATIENTS WITH DUODENAL ULCERS AND SO-CALLED PYLOROSPASM *

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THE equivocal value of analyses of gastric contents in the study of peptic ulcer is probably due to the lack of uniformity of the findings resulting from the use of the ordinary test meals. Such studies on gastric secretory function have been concerned almost entirely with the measurements of the response to a stimulus in the form of some type of a test meal or, more recently, to the injection of histamine. The response is determined by the amount of acid, of chloride and of pepsin recovered in the stomach contents. The widely divergent results of these observations have naturally aroused so much doubt as to their significance that clinicians now are growing less inclined to rely upon them for diagnostic aid.

There is probably a physiological explanation for this state of affairs. Analyses of the older as well as of the more recent studies as to the nature of the acidity found in the stomach have indicated that we are dealing with two distinct mechanisms: first, the secretion of a highly acid juice by the gastric glands; and second, its neutralization in the stomach to the level that is usually found and which is presumably acceptable by the duodenum. The actual acidity found at any time is the resultant of these two factors. The conception of some neutralizing mechanism followed directly from the observation of Pavlov,[1] of Carlson [2] and of many others that pure gastric juice as actively secreted by the stomach is approximately 0.5 per cent hydrochloric acid, whereas after the usual stimuli the gastric contents have a value of about 0.1 per cent hydrochloric acid. The fact that the chloride concentration remains the same in both instances suggested that it was not a question of secretion alone but of secretion plus neutralization. That a neutralizing factor does occur and plays a rôle in the determination of gastric acidity seems more or less generally accepted. About the mechanism of the neutralizing factor there is still some dispute.

Regardless of how the high acidity of the freshly secreted juice is neutralized, it seems obvious that a method of actually measuring the ability of the stomach to do so might prove of considerable value. Such a procedure is, in fact, easy to carry out. One simply introduces into the stomach a solution of 0.5 per cent hydrochloric acid (the strength of pure gastric juice) and measures the rapidity and degree to which it is finally neutralized. In this way, one attempts to avoid the double response (secretion plus neutralization) which is measured in the usual test meal and thus to study the effect of the neutralizing factors alone. Such a neutralization test was carried out on a series of 34 patients, some of them clinically normal and

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others with clinical evidence of gastrointestinal disease. The test is considered not as a diagnostic but merely as a functional one. It is hoped that it may yield results helpful in the understanding of the complex nature of gastric physiology, particularly in regard to the important problem of what governs the degree of acidity in the stomach contents.

Previous Work

The first studies of the regulation of the gastric acidity by a neutralizing mechanism originated in Pavlov's [1] laboratory. One of his pupils, Boldyreff [3] claimed that it took place by regurgitation of alkaline pancreatic juice. MacLean [4] and McCann [5] have recently attacked this theory on the basis of their own work, the former claiming that it is controlled in the stomach itself. Bolton,[6] on the other hand, has advanced evidence in favor of Boldyreff's theory. The results of other experiments, too, notably those by Elman and his coworkers [7, 8, 9, 10, 20] and Olch,[11] have pointed to the correctness of Boldyreff's conception. Roberts,[12] Morton,[13] Portis and Portis,[14] and more recently Matthews and Dragstedt,[21] have published data favoring this same point of view.

The use of an acid solution as a test meal was initiated by Boldyreff to measure neutralization in the stomach of dogs. It was used by Apperly [15] in humans, and with modifications by MacLean [4] in a series of interesting cases. W. L. Palmer [16] has also introduced acid into the human stomach but only to determine its effect on the production of pain. He has not reported measurements of its neutralization. Olch [11] has used this type of test meal experimentally to show the effects of various operations on gastric acidity. Elman [8] most recently used it in the study of a series of patients with duodenal ulcer, both before and after gastro-enterostomy. He found that there was a definite delay in the neutralization and in the emptying of the stomach in patients with ulcer. He attributed this to the interference by the pylorus with the normal duodenal regurgitation and, hence, with neutralization. On the other hand, he found that soon after operation the acid introduced into the stomach was promptly taken care of. The rapid neutralization was explained by the ready access of the duodenal secretions to the stomach through the new gastro-enterostomy stoma.

Method

The technic described by Elman [8] has been followed in this work. The patient was prepared as for an ordinary Ewald test meal. A small duodenal tube was passed and the fasting contents of the stomach aspirated. A slightly stronger acid was used in the present observations (0.6 per cent hydrochloric acid, or a titration figure of 160°). Three hundred cubic centimeters of the 0.6 per cent hydrochloric acid were introduced into the stomach by means of the tube. Twenty cubic centimeters were removed every 20 minutes thereafter until specimens were no longer obtainable, or

in any case, for no longer than three hours. To be sure of the removal of a fair sample, the syringe was filled and emptied several times while attached to the tube to mix the gastric contents thoroughly, after which a specimen was aspirated for analysis. Patients were instructed not to swallow the saliva but to expectorate it. Titration was carried out with tenth-normal sodium hydroxide for free and total acidity on each specimen removed, using Töpfer's reagent to determine an end point for the former and phenolphthalein for the latter. Only the total acidity is recorded on the charts.

In all but one of the cases here reported, ordinary Ewald test meals were also done. After the fasting contents were removed, the patient was given two pieces of bread and two glasses of water and 15 minute fractional specimens withdrawn for titration. The 45 minute specimen completed the test. The fractional tests were titrated for free and total acidity. On the tables, for simplification, only the 45 minute specimen is recorded. This represented the highest acidity developed. All but two patients also had a complete gastrointestinal series. The usual barium meal was given on a fasting stomach and both fluoroscopic and radiographic examinations made. Six hour and 24 hour observations were made and the patient given a cathartic to eliminate the barium from the gastrointestinal tract. The gall-bladder dye was given on the second night and 12 hour, 16 hour and 20 hour films taken. A barium enema was given under the fluoroscope and films made. A film of the appendix area was taken six hours after the barium enema. In many, operation was performed and served as a check on the roentgen-ray and clinical diagnosis.

Findings

The observations were first started on an unselected group of 60 consecutive patients complaining of gastrointestinal symptoms admitted to the Missouri Pacific Hospital, St. Louis. The data were collected objectively without regard to their interpretation. In all, 34 patients were available for the present study. Many of the remainder left the hospital before their examinations were finished. Others did not have roentgen-ray studies. Still others were isolated cases such as painless jaundice, cirrhosis of the liver, irritable colon, secondary lues, etc. It is planned to report them later as sufficient numbers of similar cases accumulate. The results were then analyzed and it was soon apparent that in general these 34 cases fell into four groups, each showing the same or similar clinical pictures (tables 1, 2, and 3) which were then compared with their respective neutralization response (text figures 1, 2, 3, and 4). Analyses of these neutralization responses showed striking similarities in their respective groups.

The first group comprised eight cases which either showed few or no significant symptoms of gastroduodenal disease, or had come in for other complaints (table 1). Roentgen-ray study of these patients likewise re-

TABLE I

Clinical Summary of Eight "Normal" Cases Whose Neutralization Curves Are Shown in Text Figure 1; Note Diversity of Ewald Meal Figures as Compared with Constancy of Neutralization Curves

Case		Complaint	Relieved by	Examination	X-Ray	5 Hr. Residue	Operation	Ewald Meal	Remarks
No.	Age								
1	30	"Nervous"	—	Negative	No evidence of organic disease	—	—	44°	Considered as a malingerer.
2	?	Many varied symptoms—not referable to any one system	—	Negative	No evidence of organic or functional disease	—	—	73°	Suspected of malingering to collect insurance
3	36	No complaints; in hospital for check-up	—	Negative	Distance between pylorus and cardia shortened as by scar tissue contraction of healed ulcer of lesser curvature	—	—	31°	In hospital 4½ mo. before for an acute bleeding ulcer. Conservative treatment with clinical and x-ray cure. Symptom-free 4½ mos. Stools negative for occult blood. No recurrences one and one-half years later.

TABLE I (*Continued*)

Case		Complaint	Relieved by	Examination	X-Ray	5 Hr. Residue	Operation	Ewald Meal	Remarks
No.	Age								
4	65	Diarrhea at times for past 4 yrs.; weakness	—	Liver 2 fingers below costal margin	Negative	—	—	7°	Relieved on balanced diet; regained strength.
5	60+	Anorexia; weakness	—	Negative	Negative	—	—	43°	Put on full balanced diet. Felt fine in very short time.
6	40	Gas and belching after meals; occasional diarrhea	—	Negative	Evidence of past appendiceal disease now negative	—	—	10°	No clinical evidence of appendicitis. Roentgenologist did not consider appendix guilty.
7	?	Headache	—	Negative—error in refraction	—	—	—	7°	None
8	?	Headache; gonorrhea	—	Urethral discharge	—	—	—	—	None

TABLE II

Clinical Summary of Thirteen Cases of Probable Duodenal Ulcer as Indicated by Positive Roentgen-Ray Findings

Case		Complaint	Relieved by	Examination	X-Ray	5 Hr. Residue	Operation	Ewald Meal	Remarks
No.	Age								
9	30	Pain in pit of stomach 2½ hrs. after eating; associated with belching	Belching; eating again; soda	Slight epigastric tenderness	Small irregularity on medial wall of duodenal bulb with coinciding tenderness; second examination 6 months later showed a normal duodenum and a pathological gall-bladder	None	Pathological gall-bladder with four stones; pathological appendix; small white scar on medial border of duodenum	34°	Symptoms of ulcer disappeared; along with clinical cure there was an x-ray cure. Repeated neutralization tests showed an improvement in neutralization and emptying. Later gall-bladder symptoms developed.
10	38	Pain in stomach 2–3 hrs. after eating, occurring each spring. Sudden severe pain brought him to hospital	Soda and eating again	Pale, clammy; tender over lower abdomen	Two defects in duodenal cap and one in second duodenum. Pylorus widened	None	—	66° 85°	Emergency appendix in 1920. Ulcers seen at operation but condition precluded doing anything to them. History dates back 26 years.
11	41	Epigastric discomfort 2–3 hrs. after meals	Eating; soda	Negative	Duodenal cap small and deformed	None	—	80°	X-ray and clinical diagnosis of uncomplicated duodenal ulcer. Duration 11 yrs. Pain produced by acid meal.
12	39	Fullness after eating. Epigastric pain 2 hrs. after eating	Eating; soda	Negative	Uncomplicated duodenal ulcer	None	—	67°	Typical history of duodenal ulcer, with x-ray confirmation. Duration, 10 yrs.

TABLE II (*Continued*)

Case		Complaint	Relieved by	Examination	X-Ray	5 Hr. Residue	Operation	Ewald Meal	Remarks
No.	Age								
13	54	Pain in stomach 1 hr. after eating made worse by greasy or acid foods	Eating; soda	Slight tenderness in epigastrium	Not definite but suspicious of duodenal ulcer	None	—	110°	History and clinical course suggest probable duodenal ulcer. Acid meal produced pain. Relief by Sippy diet.
14	29	Epigastric pain 2 hrs. after eating; worse in summer	Eating; milk; soda	Slight tenderness in epigastrium	Duodenal deformity in left lower angle with associated tenderness 2°	None	—	58°	History and x-ray findings those of probable duodenal ulcer. 2 yrs. duration.
15	28	Pain in stomach; had a sudden severe pain with vomiting of dark greenish fluid followed by collapse	Eating	Acutely ill, abdomen rigid in both upper quadrants	Defect in duodenal cap	Slight	—	90°	Under conservative treatment patient improved rapidly. Duration of symptoms 2 mos. Diagnosed as a perforating ulcer.
16	48	Severe epigastric pain associated with pallor, weakness, tarry stools, and vomiting of blood	Conservative care	Pale, acutely ill; systolic murmur at mitral area. Epigastric tenderness	Irregularity of duodenal cap	None	—	70°	Symptoms of pain in stomach 1 hr. after eating for past 10 yrs. Improved rapidly on conservative treatment and diet.

TABLE II (*Continued*)

Case		Complaint	Relieved by	Examination	X-Ray	5 Hr. Residue	Operation	Ewald Meal	Remarks
No.	Age								
17	30	Pain in upper abdomen 2 to 3 hrs. after eating. Occasional vomiting	Food; soda	Tender in epigastrium	Conclusive evidence of duodenal ulcer	None	—	51°	Three different observers made x-ray diagnosis of duodenal ulcer. 13 yrs. duration.
18	35	Bloating, belching and pain 1½ to 2 hrs. after eating	Soda; magnesia	Tender in epigastrium	Duodenal deformity characteristic of ulcer	None	—	71°	One year's duration.
19	21	Hunger pain; worse in summer	Food; soda	Negative	Duodenal deformity suggestive of ulcer	None	—	43°	1½ yrs. duration. Probable duodenal ulcer
20	24	Burning in stomach one hour after eating	Belching; soda	Slight epigastric tenderness	Duodenal deformity characteristic of ulcer. Also a pathological appendix	Slight	Refused	82°	History of several attacks suggestive of hemorrhage from ulcer.
21	49	Pain in epigastrium 2 hrs. after eating, made worse by acid foods. Vomiting. Worse each fall	Eating; soda	Tender in epigastrium	Gall-bladder normal. Duodenal cap showed deformity characteristic of ulcer	None	—	92°	Typical history of duodenal ulcer. Duration 12–15 yrs.

TABLE III

Eleven Cases of Presumed Pylorospasm. Appendiceal Disease Characterized This Group with Definite Ulcer Symptoms

Case		Complaint	Relieved by	Examination	X-Ray	5 hr. Residue	Operation	Ewald Meal	Remarks
No.	Age								
22	32	Soreness under ribs associated with nausea	Food, slightly	Slight tenderness in right lower quadrant	No duodenal deformity. The gall-bladder was not visualized	—	Subacute appendix. Stomach, duodenum, gall-bladder normal	75°	Oral administration of gall-bladder dye, symptoms 2 yrs., relieved by operation.
23	?	Bloating one hour after eating. Pain in epigastrium 2 hrs. after eating	Eating again; especially milk	Slight tenderness in epigastrium	Stomach and duodenum normal; appendix pathological; irritable 80°	—	Refused	59°	Two weeks' duration.
24	29	Epigastric pain 2 hrs. p.c.; radiating to chest and back; made worse by heavy and greasy foods	Eating again	Tender in epigastrium	Slight irregularity of pylorus (inner border). Repeat 3 wks. later:— Stomach and duodenum normal, appendix tender, 3°, with guard over it	Slight None	Subacute appendix. Stomach, duodenum and gall-bladder normal	62°	Duration 1½ yrs. Almost typical history of duodenal ulcer.
25	?	Epigastric pain 2 hrs. after eating	Soda; eating	Tender in epigastrium and over McBurney's point.	Stomach and duodenum normal, slight increased motility; gall-bladder normal; appendix definitely pathological, 70°	None	Refused	70°	Duration 1½ yrs. Pain reproduced by acid meal.

TABLE III (*Continued*)

Case		Complaint	Relieved by	Examination	X-Ray	5 hr. Residue	Operation	Ewald Meal	Remarks
No.	Age								
26	23	Epigastric pain 2 hrs. after eating	Belching; soda; eating	Slight epigastric guard	Active gastric peristalsis with normal pylorus and duodenum. Appendix tender, kinked	—	Stomach, duodenum, gall-bladder normal. Appendix kinked, retrocecal, chronically involved	91°	X-ray diagnosis = pylorospasm and pathological appendix. 2 mos. duration. Operation relieved symptoms.
27	44	Epigastric pain 1–2 hrs. p.c. Worse each spring and fall	Eating; soda	Slight tenderness in mid-upper abdomen	Stomach, duodenum, gall-bladder normal. Appendix kinked and tender	Marked	Stomach, duodenum, and gall-bladder normal; subacute appendix	36°	History typical of duodenal ulcer; including seasonal periodicity; poor relief and intolerance of certain foods. 15 yrs. duration.
28	41	Epigastric pain 2 hrs. p.c. associated with acid and sour foods	Soda; bellans tablets	Tenderness and guard over McBurney's point	Stomach and duodenum normal. Tender 3° over base area of appendix	—	Stomach, duodenum and gall-bladder normal. Appendix white, waxy, thickened, buried in adhesions	74°	2 yrs. duration. Clinical, x-ray, and operative diagnoses were pathological appendix.
29	?	Epigastric pain 3 hrs. after eating; vomiting	Eating; sodium phosphate	Negative	Slight irregularity of lesser curvature of stomach. Duodenum perfect. Appendix tender 2° and pressure over it causes the epigastric pain	—	Stomach, duodenum and gall-bladder normal. Appendix white, thickened, bound down to cecum	36°	Duration 3 yrs. Operation relieved symptoms.

TABLE III (*Continued*)

Case		Complaint	Relieved by	Examination	X-Ray	5 hr. Residue	Operation	Ewald Meal	Remarks
No.	Age								
30	?	Pain one hour after meals, increasing until patient eats	Eating; soda	Epigastric tenderness	Irregularity of pyloric end of stomach just proximal to the pylorus	—	Duodenum and stomach negative, subacute appendix	74° 68°	History of 12 yrs. duration with text-book picture of duodenal ulcer. Emergency operation for subacute appendix with relief of symptoms. Developed pulmonary tuberculosis 1½ yrs. later.
31		Epigastric pain and vomiting	Vomiting	Soft systolic mitral murmur; tender over right kidney	K.U.B. negative. G.I. and G.B. series negative	—	Duodenum, stomach, gall-bladder normal. Had a chronic appendix	41°	Eight months' duration. Relieved by operation.
32	29	Epigastric pain radiating to back	Soda; milk	Negative	Evidence of juxta-pyloric or prepyloric ulcer. Appendix pathological but quiescent. Gall-bladder normal	—	Chronic appendix buried in a well of adhesions which extended up to the gall-bladder and stomach and duodenum; stomach and duodenum normal	78°	Failed to respond to diet and alkalies, operation advised, 1½ yrs. duration. Removal of appendix relieved patient of all symptoms. Followed one year after operation.

vealed no gastroduodenal lesion. They all showed curves which agree with those reported by Elman [8] in a series of normal adults. These cases therefore were taken as a control group for the others.

The second group includes 13 patients in whom evidence of duodenal ulcer was found either by roentgen-ray examination or by operation, or both (table 2). The neutralization curves show a longer, more gradual drop than in the normal (text figure 2) which agree with those reported by Elman [8] in his cases of duodenal ulcers proved at operation. My curves

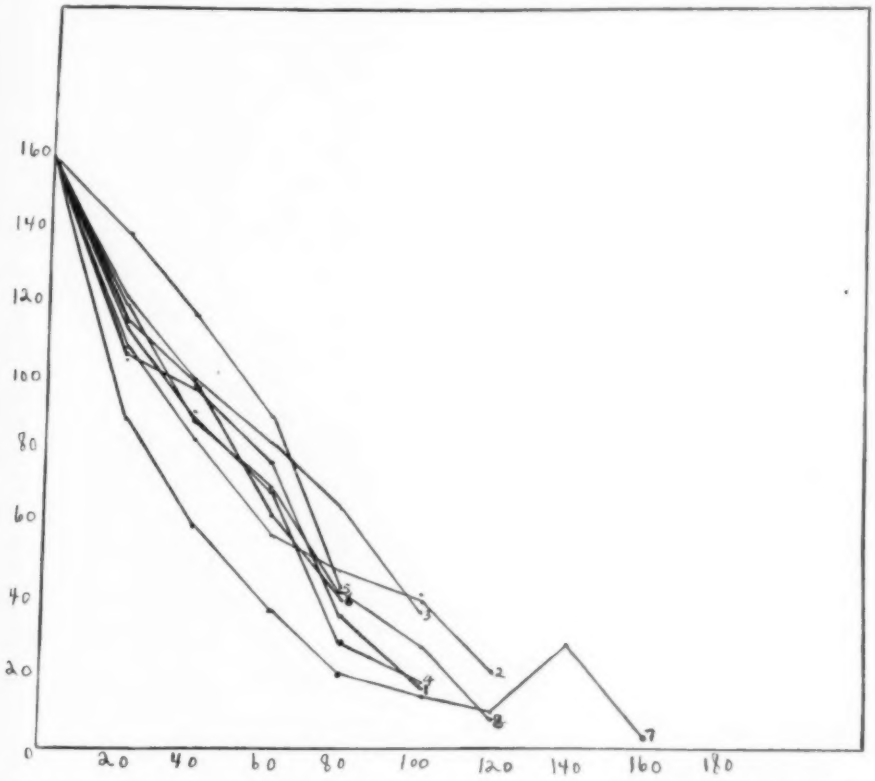

FIG. 1. Eight "normal" neutralization curves. Clinical findings normal (table 1).

are in general more prolonged, indicating not only a more delayed neutralization but also, in some, a more delayed emptying. These differences may be due to the use of the higher acid in the test solutions in my cases (0.6 per cent hydrochloric acid instead of 0.5 per cent). It will be noted that in only two of my patients was typical pain reproduced during the test (cases 11 and 13, table 2). In contrast to this observation, Palmer [16] found that pain was produced by the acid meal in practically all of his patients who were examined during the period in which they were subject to spontaneous pain. This may be explained partially by differences in technic, for Pal-

mer [16] aspirated the stomach at the end of 30 minutes if no pain had been produced and re-introduced the hydrochloric acid, repeating this a third time before considering the test negative.

The third group represents 11 patients who had a more or less characteristic symptom picture of duodenal ulcer but without any objective findings thereof. Some showed a definite gastric residue after the barium meal. All had roentgenological or operative findings of appendiceal disease (table 3). In nine operated upon, a pathological appendix was removed. Nearly

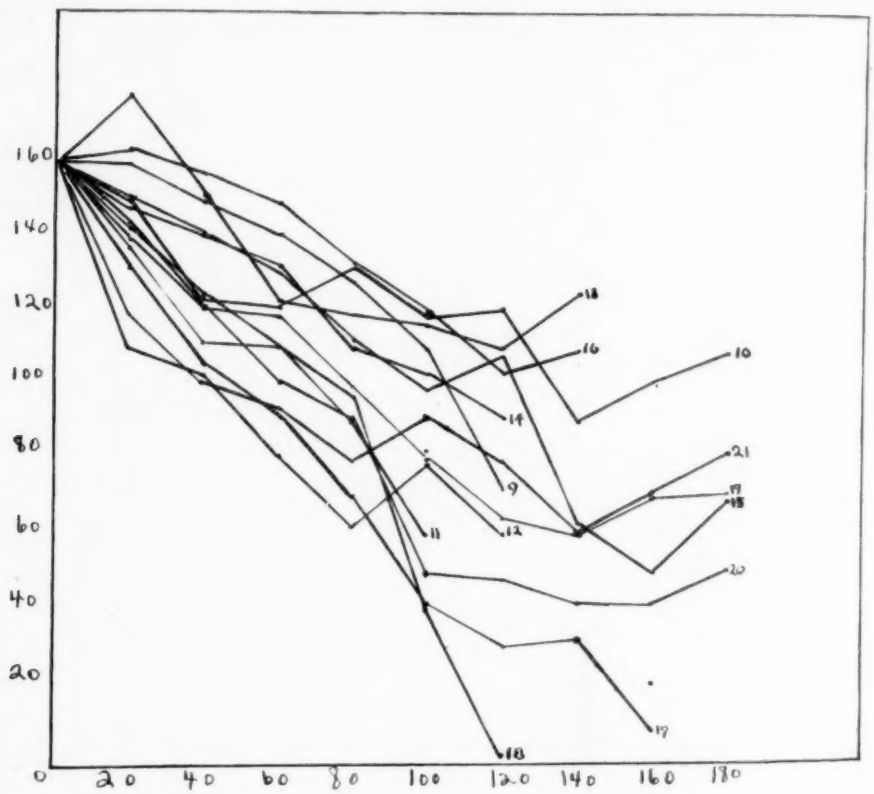

FIG. 2. Thirteen cases of probable duodenal ulcer (table 2).

all were followed for various periods after operation and found to have been relieved of their symptoms. Their neutralization curves (text figure 3) agreed in general with those of the duodenal ulcer cases of the second group.

These patients in the third group have been tentatively assumed to have a pylorospasm, even though I realize how difficult it is to be sure of such a diagnosis and also how inaccurate such a designation may be. Nevertheless, in the absence of any objective ulcer the diagnosis of pylorospasm may serve a useful purpose, at least as a working hypothesis to explain the

gastroduodenal symptoms and signs. It will be noted that one patient (case 25, table 3) had his typical pain during the test, although Palmer states that the test in his hands does not produce pain in the absence of gastroduodenal ulceration. It is possible, of course, that an ulcer was present even though the roentgen-ray was negative. It is to be noticed that in general there is less variability in the curves in this group than in those of duodenal ulcers. All but two showed the same delayed neutralization. The two exceptions had approximately normal curves (cases 31 and 32). These

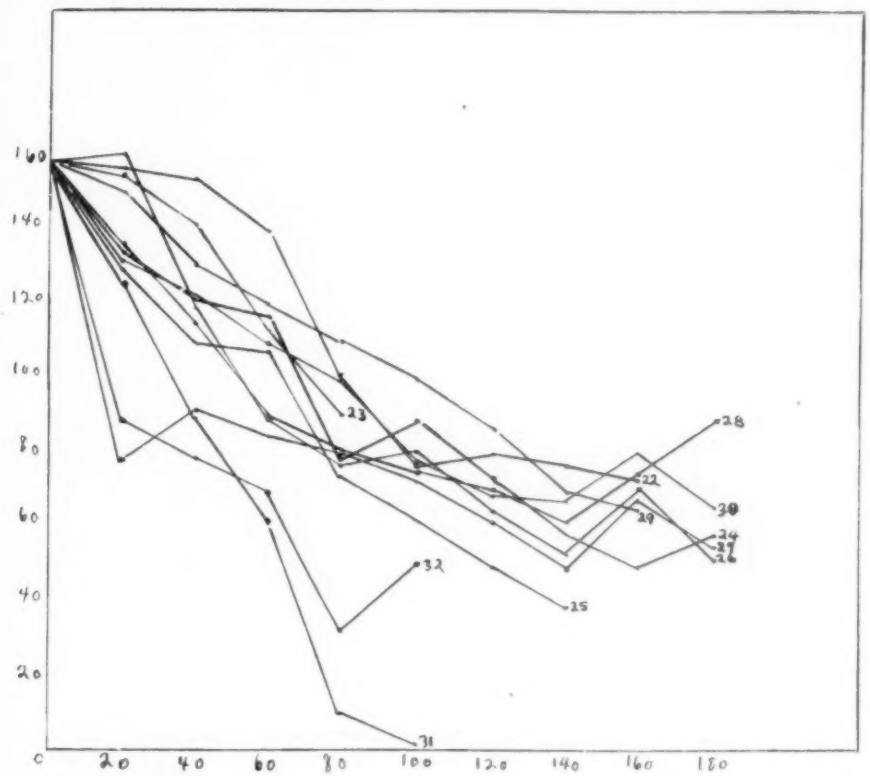

FIG. 3. Neutralization curves of eleven cases with appendiceal disease but with ulcer symptoms (due to pylorospasm?). (Table 3.)

cases differed clinically in no way from the other nine. They indicate perhaps that with pylorospasm functional abnormality as shown by this test in the other cases may at times be absent.

The fourth group comprised two cases in which a gastro-enterostomy had been performed six and 13 years before, and roentgen-ray showed both stomata functioning. They have had no gastric symptoms since their operations. The steep short curves (text figure 4) in both indicate more rapid neutralization of the test solution than in the normal and agree with similar results reported by Elman.[8] It is of considerable interest that in

these two cases the motor as well as the chemical effect of gastro-enterostomy should remain intact after so many years.

Presence of Bile. In addition to the above observations, the presence of bile in the aspirated samples was carefully watched for, although not recorded in the tables (to avoid their becoming too complex). Bile was found in 62 per cent of the normal cases, in 7.5 per cent of the group of patients with duodenal ulcers, and in 54.5 per cent of the cases of "pyloro-spasm" in group 3. This has been the experience of others. The presence of bile in gastric contents obviously means that duodenal regurgitation has

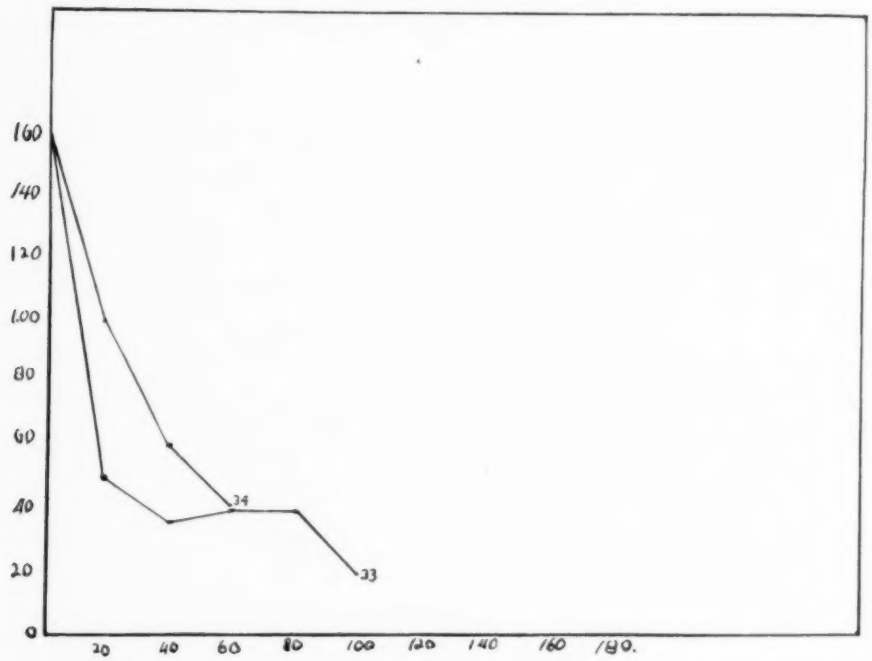

FIG. 4. Neutralization curves in two cases with gastro-enterostomy performed years before. (Cases 33 and 34; see text.)

occurred. Its significance stops here. Many steep curves (rapid neutralization) were unaccompanied by the appearance of bile. This emphasizes again the fact, often overlooked, that the absence of bile does not mean that duodenal regurgitation does not occur. Bile is discharged into the duodenum intermittently unlike pancreatic juice which flows directly and constantly into the intestine.

Ewald Acidity and Neutralization Test. Another result of these studies concerns the comparison between the neutralization curve and the acidity developed after the Ewald test meal. In general the acid meal gave more constant results. For example, the values after the Ewald test meal varied from 7° to 73° in the eight normal cases (table 1), unlike the neutralization

curves which were strikingly uniform (text figure 1). The second group (the duodenal ulcer cases) shows after the Ewald meal a higher average acidity than normal but the individual cases vary greatly (34° to 110°), three showing normal values (cases 9, 17, and 18). In contrast, the neutralization curves all showed a delay. Moreover, those with the greatest delay in neutralization did not have the highest acidity and vice versa. Thus cases 16 and 18 show the same Ewald acidity (70° and 71°) yet the neutralization curve of case 16 showed a much more marked delay than that of case 18. It is significant that the symptoms of the former were more chronic, having been present for 10 years, while those of the latter were present but for one year. This suggests that the neutralization curve reflected the severity of the disease more accurately. Again, in case 9, which had a normal Ewald acidity (36°), the neutralization curve showed a marked delay. It is of additional interest to note that under medical treatment this case improved. Repeated acid test meals reflected this improvement and finally showed a practically normal curve nine months later. (These data are not shown in the tables.) Some months after this an operation was performed for gall-bladder disease, at which time the scar of the healed duodenal ulcer was noted. Another case with a normal Ewald acidity (case 19, 40°) also showed the usual delay in neutralization observed in these cases.

In the third group labeled "pylorospasm," comparison of the neutralization curves (text figure 3) with the Ewald meal findings of the same patients (table 3) shows similar but less marked discrepancies. For example, in cases 27 and 29 with a normal Ewald acidity (both 36°) there was a definite delay in neutralization almost as marked as in the cases of actual duodenal ulcer. In both the ulcer symptoms were characteristic, of 15 years' duration, and both were relieved by appendectomy. It is interesting to note that in the two cases of this group (31 and 32) which had normal neutralization curves, the Ewald acidity in the former was normal (41°) whereas in the latter it was high (78°). One can not explain this discrepancy by the clinical picture in these two cases.

Comment

The data reported herein comprise the result of a more or less untried test of gastric or really gastroduodenal function; namely, the power of the stomach to neutralize an acid test solution placed within its lumen. Since the acidity of the test solution is that of the pure secretion of the stomach (0.5 per cent hydrochloric acid) we may infer that one measures in this way the physiological ability of the patient to neutralize his own gastric juice. The importance of this mechanism has already been briefly suggested from theoretical considerations. The findings herein recorded indicate that it may also prove of practical value in the diagnosis and prognosis of disease involving the pylorus.

It must be admitted that the criteria used to ascertain actual disease in these patients are open to criticism. Roentgen-ray examination is not an infallible diagnostic test and presumably ulcers may be present without giving any signs with the barium meal. Even actual inspection and palpation at operation may fail to show a small posterior ulcer of the duodenum. These defects are clinically unavoidable, however, and I feel are probably not a frequent source of error. At any rate the methods employed represent the most effective ones available at the present time for the objective clinical estimation of pyloric disease.

The results show that in patients with duodenal ulcer (as shown by roentgen-ray or by operation) there is an inability to neutralize the test solution as promptly or as completely as in the normal. They also show a delay in emptying the stomach. The same type of curve is found in patients having a similar symptomatology but without objective roentgen-ray or operative evidence of ulcer. These patients were assumed to have a spastic pylorus as shown by the occurrence of a gastric residue in some and by the similarity to ulcer symptoms. They all had evidence of appendiceal disease and all but two cases were operated upon and relieved of ulcer symptoms by appendectomy.

The impaired gastric neutralization found in these two groups of cases with actual or presumed pyloric disease suggests that the high acidity so often found in these cases is due not entirely, if at all, to hypersecretion but probably to faulty neutralization. These findings can be explained by the theory that regurgitation of alkaline duodenal contents is diminished in these conditions and that as a result there is the faulty neutralization. But whatever the explanation, there seems no doubt from my observations that the stomach in these cases is not as well equipped to reduce acidity as is a normal organ.

The fact that one rarely finds as high an acidity in the stomach as in the gastric juice which is actively secreted by the gastric glands cautions one against the use of the term hyperacidity. One should more properly speak of a defective neutralization since pure gastric juice is probably always secreted at the same degree of acidity. According to this conception one should prefer the use of the term hyponeutralization to describe the finding of high acid values rather than hyperacidity, since it is clear that the gastric glands can never secrete above the level of about 0.5 per cent hydrochloric acid. This level is rarely, if ever, found in the analysis of ordinary gastric contents. On the other hand, in cases of low acidity we are probably dealing with an effective or a very rapid neutralizing power and perhaps should speak of these cases as instances of hyperneutralization rather than of anacidity, provided of course that we exclude those cases of actual inability of the gastric glands to produce a normal secretion.

The bearing of the present findings on the question of the pathogenesis of duodenal ulcer is significant in that they point to the importance of the acid factor. The work of Elman,[10] Morton [13] and Mann [18] shows that

drainage of the duodenal or pancreatic juices into the lower intestine or to the outside leads to the production of experimental ulcers. It has been shown that these procedures result in a high acidity [7, 21] arising from defective neutralization, which may thus be a significant factor in the etiology of ulcer. The observations of Apperly and Cameron [15] and of Bolton [19] also emphasize the conception that a deficiency in the neutralization process is the essential cause of so-called "gastric hyperacidity." A recent report by Elman and Eckert [20] shows that a high acidity may be produced experimentally by pyloric closure or stenosis. The mechanism in man may be a neuromuscular irritability preventing the reflux of the duodenal juices into the stomach, or a duodenitis impairing anti-peristalsis, or a definite decrease in the neutralizing power (or alkalinity) of the pancreatic juices. To the best of my knowledge, the latter has not been thoroughly investigated and is worthy of study.

The variability of the acidity after the Ewald meal in the above cases is not surprising when one considers the double significance of this measurement, since there is involved in this test a stimulus to secretion as well as neutralization. The secretory response of the stomach is notoriously variable, dependent as it is on psychic and other subjective factors. On the other hand, the neutralization test with the acid meal depends on a single mechanism and probably gives a clearer idea of the function of the stomach in the individual case. This undoubtedly explains the greater uniformity of the findings after its use. While limited in number, the present observations seem promising enough to warrant its further use in gastro-enterology.

Summary

1. An acid test solution (0.5 per cent hydrochloric acid) was used to study the gastric neutralization in 34 patients and the results were correlated with the clinical picture, roentgen-ray and operative findings.

2. A definite diminution and prolongation of the neutralization rate was found, as compared with eight normals, in 13 cases of duodenal ulcer and 11 cases of "pylorospasm" (patients with ulcer syndrome but with pathological appendix, and relieved of symptoms by appendectomy).

3. As compared with the gastric acidity following the standard Ewald test meal, the neutralization test showed a greater uniformity and in general a closer correlation with the physical and clinical findings and it would seem, therefore, to be of greater diagnostic importance.

4. The conception of hyponeutralization rather than hyperacidity was discussed.

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ACQUIRED HEART BLOCK WITH ADAMS-STOKES ATTACKS DEPENDENT UPON A CONGENITAL ANOMALY (PERSISTENT OSTIUM PRIMUM) *

REPORT OF A CASE WITH DETAILED HISTOPATHOLOGIC STUDY

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HEART block due to or dependent upon a congenital anomaly of the heart is rare. Acquired heart block of this kind is even more rare than congenital heart block. Forty-four accepted cases of congenital heart block have been collected from the literature by Yater, Lyon and McNabb,[1] which include a new case studied histopathologically by these authors. In their review they state that patent interventricular septum was the diagnosis, either clinical or postmortem, in 26 cases. Necropsies were performed, however, in only five of the 44 cases, and in only three of these were histopathologic studies of the conduction system made. In four of the five cases studied postmortem the heart block was due to a defect in the interventricular septum, and in the fifth case Yater [2] showed the heart block to have been due to complete separation of the atrioventricular node from the bundle of His by the central fibrous body in a heart in which all parts were transposed except the ventricles.

A search of the literature has failed to reveal any detailed reports of acquired heart block due to or directly associated with a congenital anomaly of the heart. The only references in this connection we have been able to find are those of Laubry and Pezzi [3] and of Giroux and Katsilabros.[4] Laubry and Pezzi state that cases of heart block have been observed by them to be due to sclerosis at the border of interventricular septal defects, the sclerosis apparently compromising the function of the bundle of His. They cite the case of a woman aged 57 years whose pulse rate was 30 to 35 per minute and who had had dizzy spells for a short period. At necropsy they found a large septal defect with thick fibrosis of its edge in the presumed region of the bundle of His, but a histologic examination was not made. Giroux and Katsilabros refer to this reference and add the name of Marcel Labbé in the same connection, but they fail to give the bibliographical reference of the latter's work, which we are unable to find. Amberg and Willius [5] report the case of a girl aged five years in whom au-

* Received for publication, November 8, 1933.
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† Deceased.

ricular flutter and a varying degree of heart block were associated with a widely patent foramen ovale and a greatly dilated but apparently not diseased right atrium. The following case is apparently the first case to be reported in detail of acquired heart block dependent upon a congenital anomaly. According to Maude E. Abbott [6] it is also one of the few cases of persistent ostium primum in which the course of the conduction system has been traced by serial sections.

Case Report

History. The patient, a white woman aged 57 years, was first seen in August 1929 because of frequent attacks of light-headedness and loss of consciousness, which had begun after an attack of influenza eight months previously. These attacks were most likely to come on awakening in the morning or while eating, especially at breakfast. Excitement would often provoke them, and then there would be palpitation. She did not have dyspnea, cough, edema or change in heart rate. At the age of 12 years she had had "rheumatism," after which she was in robust health and gave birth to five children. At the age of 30 she had typhoid fever, after which she was confined to bed for several months with a "leaky heart and liver and heart dropsy." From then until admission, a period of 30 years, she had remained thin and frail. Twelve years before admission she had been told by a physician not to take digitalis, since she had a "digitalis heart." Physical examination revealed an undernourished woman

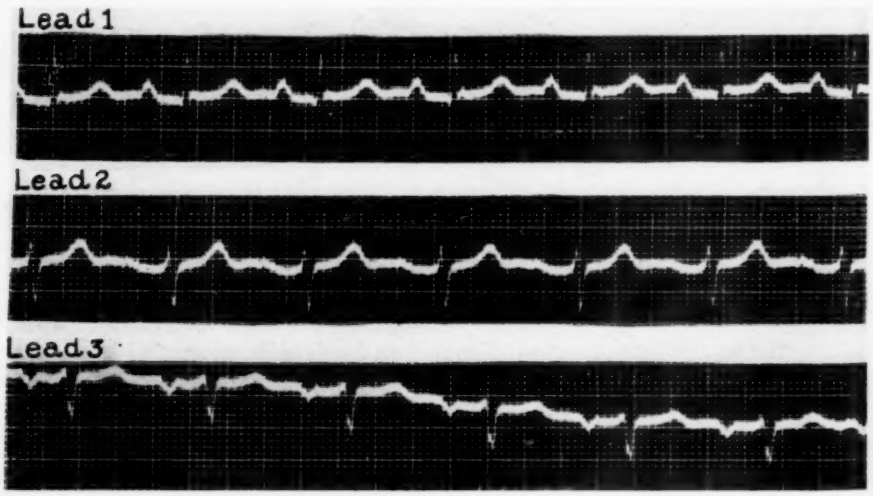

Fig. 1. Electrocardiogram made August 6, 1929, showing delayed atrioventricular conduction (prolonged P–R interval) and inverted P-wave in Lead III.

with a blood pressure of 144 systolic and 100 diastolic and the heart beating regularly 86 times per minute. The heart was greatly enlarged, especially to the left. There was a loud systolic murmur heard over the entire precordium with a diastolic murmur confined to the apex. The lungs were clear and the liver was not enlarged. There was slight cyanosis but no clubbing of the fingers. A prolonged P–R time was noted in the electrocardiogram (figure 1). Fluoroscopic examination showed enlargement of the heart slightly to the right and rather markedly to the left, the shape suggesting a mitral lesion. A tentative diagnosis of intermittent heart block with Adams-Stokes

attacks and mitral valvular disease was made. She did not accept treatment for the next 14 months except ammonia for relief of attacks. She was next seen in October 1930 with a heart rate of 32 and a blood pressure of 90 systolic and 45 diastolic. The loud systolic murmur was synchronous with ventricular systole, and was heard 33 times per minute, but three loud diastolic murmurs were heard at the apex between ventricular beats. There were long periods of asystole with unconsciousness, during which the apical murmur, previously timed as diastolic was heard at the usual heart rate. The electrocardiogram showed total atrioventricular dissociation (figure 2).

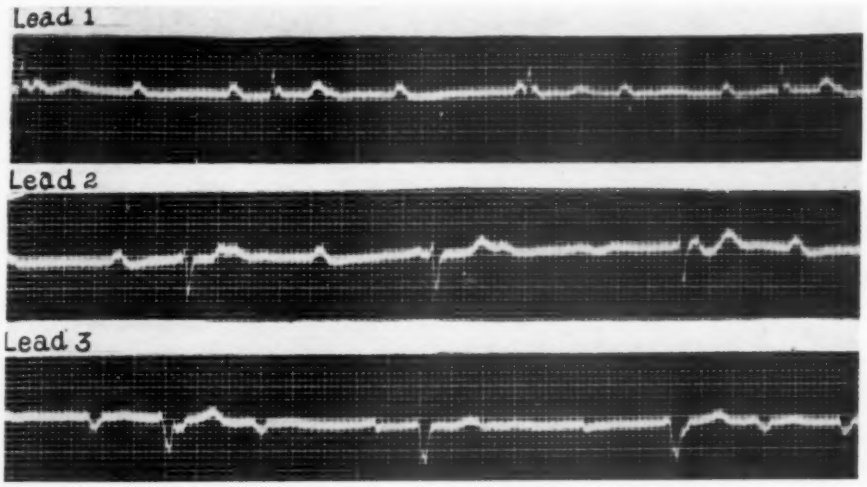

FIG. 2. Electrocardiogram made October 10, 1930, showing total atrioventricular dissociation, the P-wave in Lead III still being inverted.

There were periods, however, of 1-to-1 rhythm, but these were followed at times by Adams-Stokes attacks, with extreme sinus slowing as well as atrioventricular heart block (figure 3). Five months later (April 28, 1931) she reported again. The

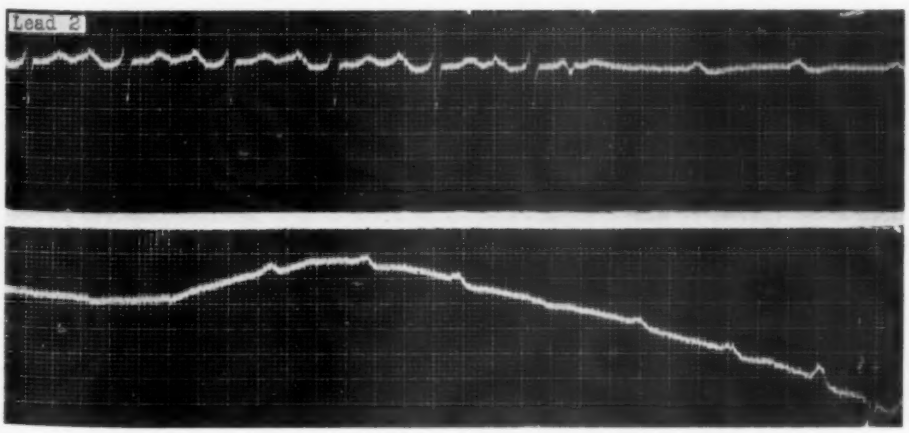

FIG. 3. Continuous electrocardiographic tracing made October 11, 1930, showing a period of atrioventricular heart block or ventricular standstill with sinus bradycardia, beginning after an ectopic atrial beat.

syncopal attacks and giddiness had continued, always worse in the morning and after eating. Frequently she was unconscious for a few seconds or a minute or two. During the longer spells unconsciousness was intermittent. Atropin seemed to control the spells but required progressively increasing doses, now 1/100 grain every four hours, and oftener when attacks were frequent. The pulse rate was 60 to 64 and fairly regular at this time. After the administration of 1/50 grain of atropin the pulse rate rose in two hours to 96 and remained between 76 and 88 for three hours more, after which it dropped to 42 and became irregular. The administration of 10 minims of adrenalin then made the rate increase to 100. For the next two months she was under close observation and various studies were made. The attacks continued in spells. Sometimes the pulse rate was 85 to 90, but most of the time when taken it was 40 to 44, sometimes a little lower, sometimes a little higher. An electrocardiogram on June 2, 1931 showed heart block shifting from 2-to-1 to 3-to-1. The attacks were fewer when the patient was taking 3/4 grain of ephedrin four times a day. The administration of barium chloride, 1/2 grain four times a day, seemed to have no effect. On June 15, 1931, the electrocardiogram revealed complete heart block. Total dissociation was always present from that time on when electrocardiograms were made. The effect of thyroid extract, two grains twice daily, was studied for two weeks. The attacks were much less frequent for a while but then became more frequent and worse than ever. Finally, in July 1931, severe attacks occurred several times a day and relief was not obtained from atropin or adrenalin. The liver seemed to be enlarged, but there was no edema, cyanosis or general venous congestion. On July 29, 1931, death followed a prolonged attack of syncope with convulsions.

Macroscopic Examination of the Heart. Besides passive congestion of the lungs and liver there was nothing of note at necropsy except in the heart. The weight of the heart was 505 grams. The right chambers made up the greater part of the bulk. The anterior surface was composed almost entirely of the right ventricle. The right ventricle, right atrium and pulmonary artery were much larger than normal, while the left ventricle and aorta appeared to be reduced in size. The epicardium was normal except for a filmy, fibrinous exudate over certain parts of the right ventricle. The pulmonary and aortic valves appeared normal when looked at from above. The tricuspid orifice easily admitted the tips of four fingers, but the mitral orifice did not admit the tip of the little finger. The left atrium had two large pulmonary veins, one at each lateral pole, and two smaller veins just below the right main pulmonary vein. Looking down from above through the opened right atrium a large defect in the lower part of the interatrial septum was seen just above the atrioventricular valves; it had a curved upper edge and measured about 1.7 cm. in its vertical dimension and about 3.2 cm. transversely. The fossa ovalis lay just above this and the foramen was closed. The cavity of the left ventricle was small, that of the right large. The orifice of the coronary sinus had no Thebesian valve; it measured 1.3 cm. in diameter. The posterior extremity of the interatrial defect was 0.8 cm. below the inferior margin of the orifice of the coronary sinus and directly above the posterior limit of the medial cusp of the tricuspid valve (figure 4). The portion of the interatrial septum between the defect and the orifice of the coronary sinus was thin and fibrous. The lower margin of the defect was made up of the medial cusp of the tricuspid valve itself, which passed through the defect and was continuous with the anterior segment of the mitral valve. The normally free edge of the septal cusp of the tricuspid valve was attached in its whole length to the upper edge of a slightly defective interventricular septum. This leaflet was 3.5 cm. long and 2 cm. wide. The anterior and posterior components of the tricuspid valve appeared normal and together measured 9.5 cm. in length. The tricuspid valve measured, therefore, 15.5 cm. The mitral valve was anomalous. The anterior leaflet, which was continuous with the septal cusp of the tricuspid valve, was split down its middle from attachment to free edge (figure 5.) Where the tricuspid

and mitral valves joined above the interventricular septum this common valve was attached to the upper edge of the septum by several stout chordae tendineae measuring from 0.5 to 1 cm. in length. The split anterior segment of the mitral valve presented much thickened edges along the line of cleavage. In the unopened heart the two halves of this segment greatly overlapped each other, the valve being quite redundant

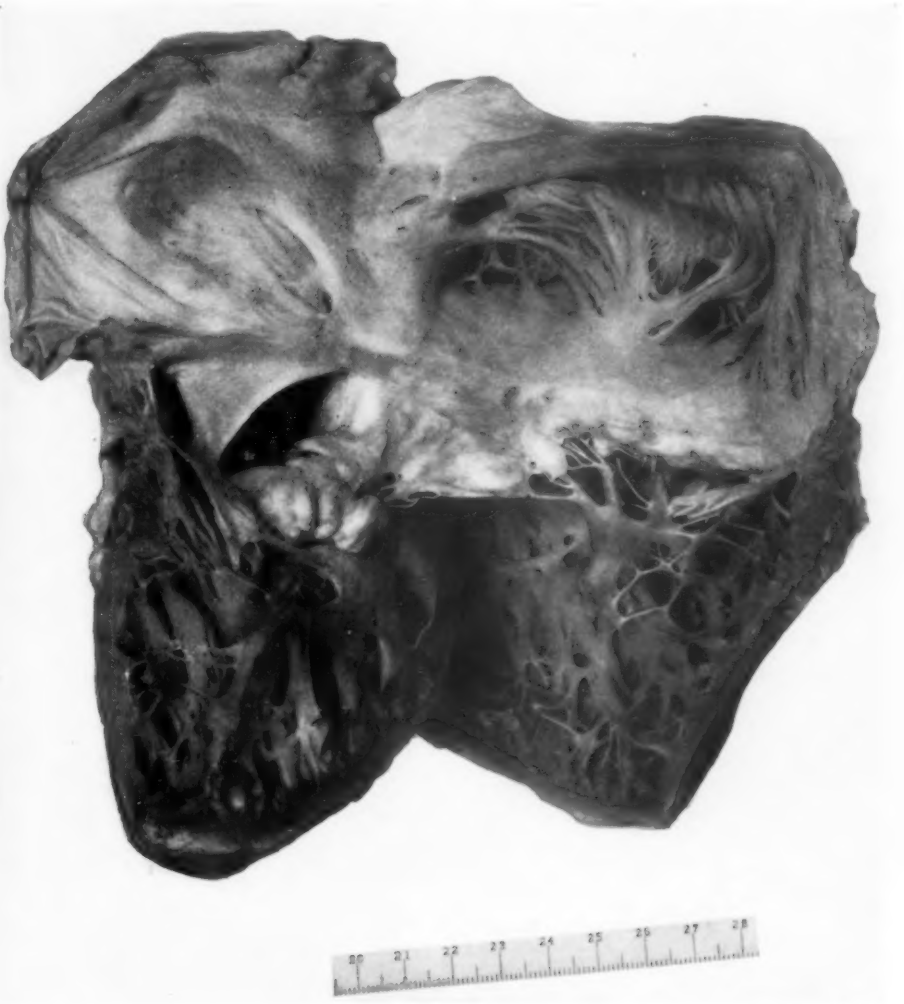

FIG. 4. Interior of the right atrium and ventricle, showing the interatrial defect (persistent ostium primum) with the medial segment of the tricuspid valve passing through it to join the mitral valve.

and itself seemingly obstructing the mitral orifice. The posterior segment of the mitral valve appeared normal. The mitral valve when opened out measured 8.5 cm., but this figure does not represent the size of the mitral orifice, which was about half this figure. The ventricular portion of the heart did not appear abnormal except for the following points. Trabeculation was very prominent in the right ventricle, while the cavity of the left ventricle had relatively smooth walls. The anterior papillary

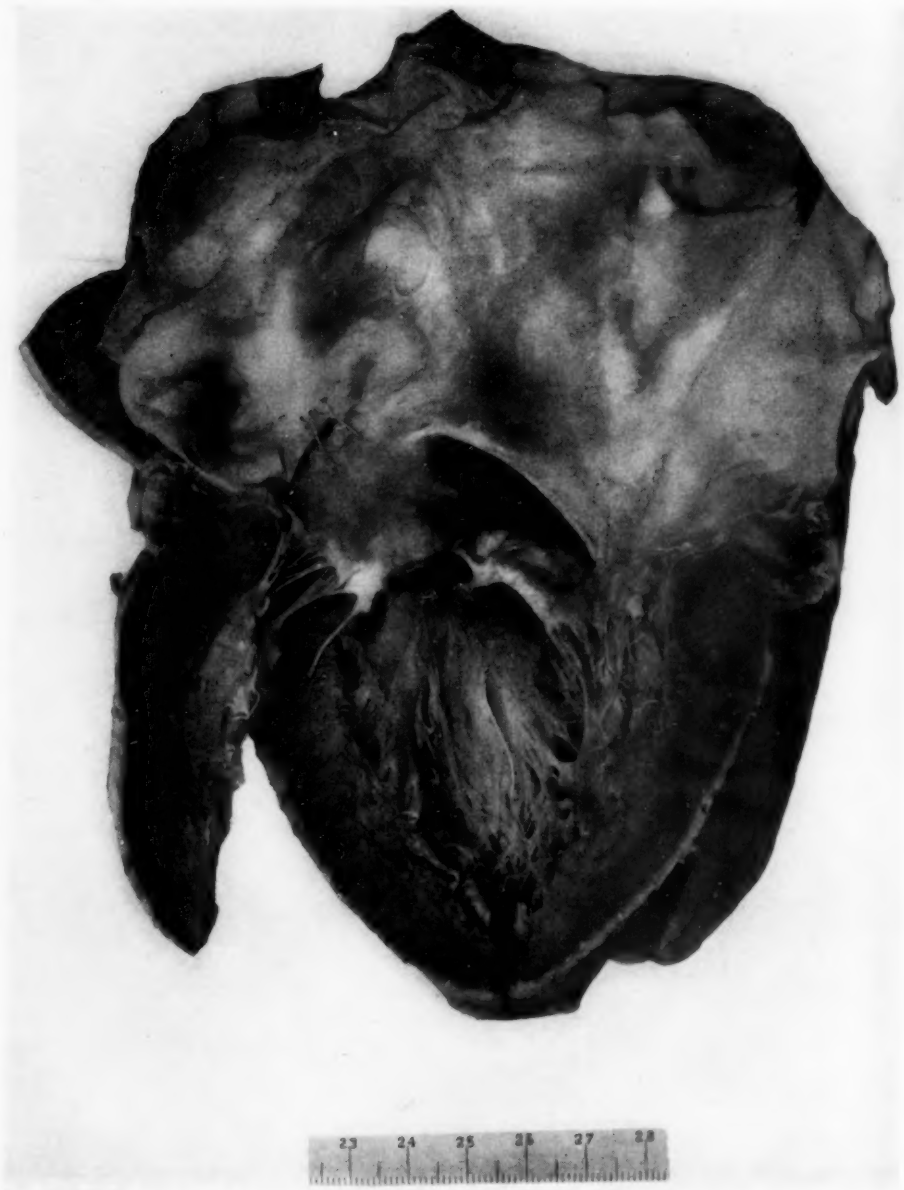

FIG. 5. Interior of the left atrium and ventricle, showing the interatrial defect and the split anterior segment of the mitral valve with a short, thick, chorda tendinea attaching it at its base to the upper edge of the slightly defective interventricular septum.

muscle of the left ventricle was about three times as large as the posterior. The muscle of the interventricular septum reached up anteriorly to the line of attachment of the aortic valve along the base of the right and left coronary cusps. The pulmonary and aortic valves appeared normal. The myocardium was apparently normal. The endocardium appeared normal also, except for some thickening and roughening in a small area, 1.5 cm. in diameter, above the posterior cusp of the mitral valve in the left atrium. The walls of the pulmonary artery and aorta were not thickened, and their intima was smooth. The coronary arteries had a normal distribution and were only slightly atheromatous. Some of the more important measurements of the heart other than those already given were as follows:

External length of right ventricle	12.5 cm.
Average thickness of wall of right ventricle	0.6 cm.
Pulmonary valve (circumference)	9.0 cm.
External length of left ventricle	7.0 cm.
Distance from middle of free edge of interventricular septum to apex of left ventricle	6.3 cm.
Thickness of left ventricle midway	1.5 cm.
Aortic valve (circumference)	5.7 cm.

Microscopic Examination of the Heart. Seven blocks of tissue were removed from the interatrial and interventricular septa for microscopic study of the main portion of the conduction system. Figure 6 shows the position of these blocks and their relative size. Study of blocks 1, 6, and 7 did not reveal any structures of interest or any pathologic changes. The main portion of the conduction system was found in blocks 2 and 3. Serial sections were made vertically through from left to right as one looks at the right side of the septum. The sections were about 8 microns thick; each twentieth one was mounted and stained with van Gieson's connective tissue stain. Intervening sections were stained when desired. The main portion of the conduction system is studied transversely by this method of examination. The atrioventricular node, the bundle of His and the first portion of each bundle branch were found and readily studied. While the location of these structures was somewhat anomalous, owing to the congenital defect, they were found where they would logically be expected. The atrioventricular node was dislocated downward so that it lay about 1 cm. below the lower angle of the opening of the coronary sinus and slightly below the attachment of the tricuspid valve. It first became apparent about section 100, block 2, and it seemed to change to the atrioventricular bundle at about section 470, block 2. It was therefore, about 4 mm. in length. It lay very close to the endocardium of the right atrium and had the usual characteristics. A relatively large arteriole accompanied it in its longitudinal axis, lying at its inner side. A relatively large venule accompanied the arteriole. Smaller arterioles and venules were seen in its substance. There was a mild degree of fibrosis of the inner half of the media of the main arteriole. The node was separated from the ventricular musculature by areolar connective tissue but lay adjacent to atrial musculature above. For most of its distance it was directly opposite the attachment of the tricuspid valve. It was anatomically different from the node of a normal heart in that it did not lie closely adjacent to the central fibrous body, which in this heart was greatly attenuated. It did not seem to contain more than the usual amount of fibrous tissue. It was broader than usual but not so lengthy in cross section. The fibers did not appear to be degenerated and there was no inflammatory reaction present. At about two-thirds along (section 400) it had its greatest dimension, and its main arteriole had become considerably larger, with a heavier adventitia. The node was more fusiform and elongated and appeared more like the normal node in shape.

In the region of section 480, block 2, the atrioventricular node began to become more condensed to form the atrioventricular bundle. The fibers at about section 540, block 2, assumed a more longitudinal direction and became parallel. In the neighbor-

hood of section 560, block 2, the bundle became surrounded by fibrous tissue, and the central fibrous body grew larger (figure 7). The main arteriole of the atrioventricular node continued along the edge for a relatively long distance. This is a distinct abnormality, since the bundle of His in a normal heart is nourished by minute arterioles only. The bundle seemed to be small, but of normal structure, until about section 780, block 2, when the number of fibers became considerably diminished and fibrous tissue invaded it. The latter had apparently spread into the bundle from the

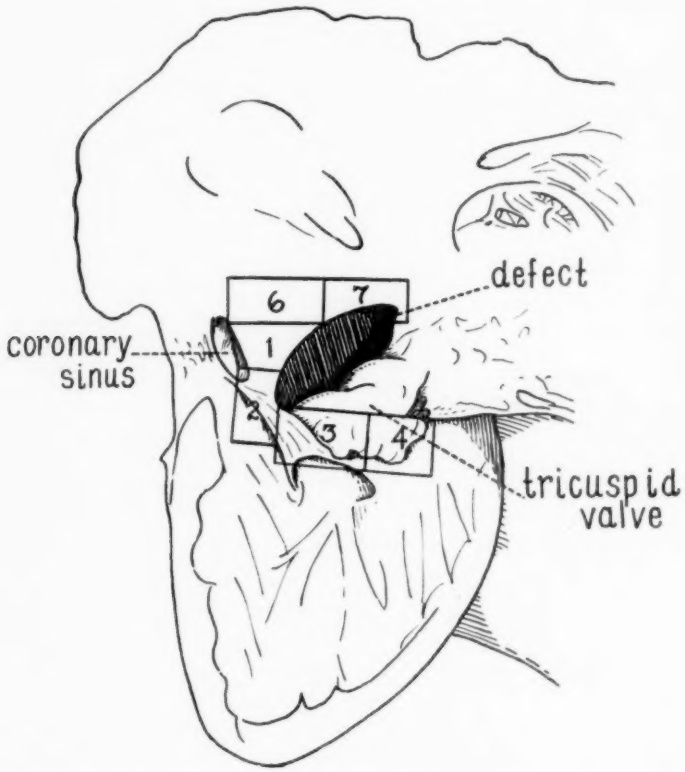

FIG. 6. Diagram of the right side of the interatrial and interventricular septa, showing the site of the blocks of tissue removed for study. Blocks 3 and 4 were cut through the entire thickness of the upper edge of the interventricular septum, the free margin of which is hidden by the tricuspid valve. Block 5, removed from the left side of the septum beneath the aortic valve, is not pictured in this view. The main portion of the conduction system was contained in blocks 2 and 3.

free edge of the interventricular septum, separating the muscle fibers and producing atrophy by compression. The bundle ran in most of its course very near the free edge of the septum, being separated from it and the attachment of the tricuspid valve by only a small amount of fibrous tissue. In the region of section 820, block 2, the amount of muscle fibers in the bundle was less than half that seen earlier in the region of section 680. The fibers seemed to become more numerous again about section 860, block 2, and the fibrous tissue was not so abundant. The fibers of the bundle, however, were not so compact. The artery was still following along one side. In the region of section 20, block 3, the fibers were arranged in small bundles with delicate fibrous tissue surrounding and separating them. These bundles became smaller and

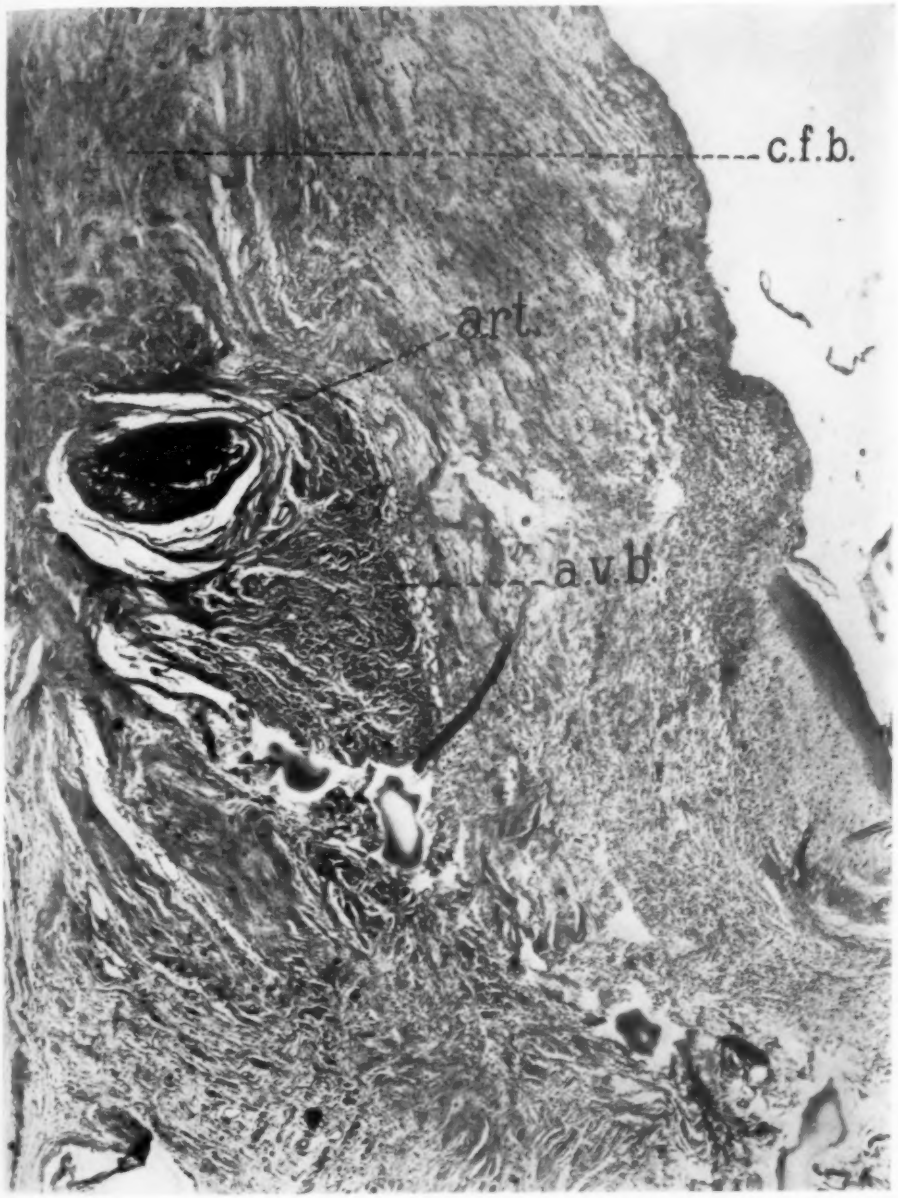

FIG. 7. Section 540, block 2, showing the relatively normal first portion of the bundle of His. *A.v.b.*, the atrio-ventricular bundle cut transversely (× 65); *art.*, the anomalous arteriole accompanying the bundle, filled with an injected bismuth and gelatine mixture; *c.f.b.*, the attenuated central fibrous body. Some artefacts are present in the lower edge of the bundle of His.

more separated for a short distance (sections 40 to 100, block 3), when they rather suddenly became more numerous and more compact. A little farther along, the bundle became considerably elongated in its cross section (section 160) and pointed at its upper and lower extremities. Soon again, however, it became less compact and more fibrotic (section 240). From sections 240 to 320 there were only a few small longitudinal bundles in it, widely separated by light fibrous tissue (figure 8). The fibers in the upper portion then became more numerous but remained separated by more than the normal amount of connective tissue. The bundle became longer in cross section up to section 460 but was still quite fibrotic, and the muscle bundles were well separated. The bundle took on the triangular shape of the crus communis at about section 520 but looked quite "moth-eaten" on account of the fibrosis and separation of the fibers (figure 9). The left bundle branch was seen to begin about section 620. The main artery which had been accompanying the bundle had broken up into three arterioles. The origin of the right bundle branch seemed to begin about section 720, at which point the main bundle was elongated transversely in cross section. The left bundle branch seemed to be normal in all subsequent sections. It had become separated from the rest of the bundle in the region of section 860, which then apparently continued on as the right bundle. The right bundle branch in the beginning was composed of small bundles of muscle fibers separated by light connective tissue. In subsequent sections it was seen lower and lower along the right edge of the section just beneath the endocardium. It retained its original characteristics for a relatively long distance, but its connective tissue was very loose and almost areolar. Its muscle fibers looked normal. It appeared to become more compact farther along (section 1380, block 3) and appeared like a perfectly normal bundle branch. The myocardium of the ventricle was apparently perfectly normal in all blocks of tissue. Blocks 4 and 5 did not reveal any abnormality. Sections of the thickened borders of the cleft edges of the anterior leaflet of the mitral valve and of the wall of the left atrium in the region of the small area of endocardial roughening above the valve showed only an old fibrosis without evidence of inflammation or of vascularization such as might have resulted from inflammation.

Summary of Pathologic Examination of the Heart. The heart was moderately enlarged, the enlargement being due to dilatation and hypertrophy of the right chambers. A large congenital defect existed in the interatrial septum, and the interventricular septum was also defective to a slight degree. The heart was a typical example of persistent ostium primum with split anterior segment of the mitral valve. The atrioventricular node was approximately normal in structure but lay lower in the right atrium than usual. The bundle of His was smaller than normal in diameter. It ran along the free edge of the interventricular septum beneath the medial segment of the tricuspid valve and the interatrial defect. A short distance from its origin in the atrioventricular node it became very fibrotic, and at several points in its course very few muscle fibers remained intact. It varied in structure at intervals but was greatly altered in all but the first portion. The bundle branches were essentially normal. The right bundle branch was longer than normal because of the large size of the right ventricle. Neither grossly nor microscopically was there indubitable evidence of previous inflammation although such was possible. There was thickening of the cleft edges of the anterior leaflet of the mitral valve and of the wall of the left atrium in the region of a small, roughened area above the valve. The coronary arteries and arterioles were not greatly altered. The myocardium appeared quite normal throughout.

Discussion

Owing to the fact that the patient had had "rheumatism" at the age of 12 years, we are unable positively to assert that the area of thickening of

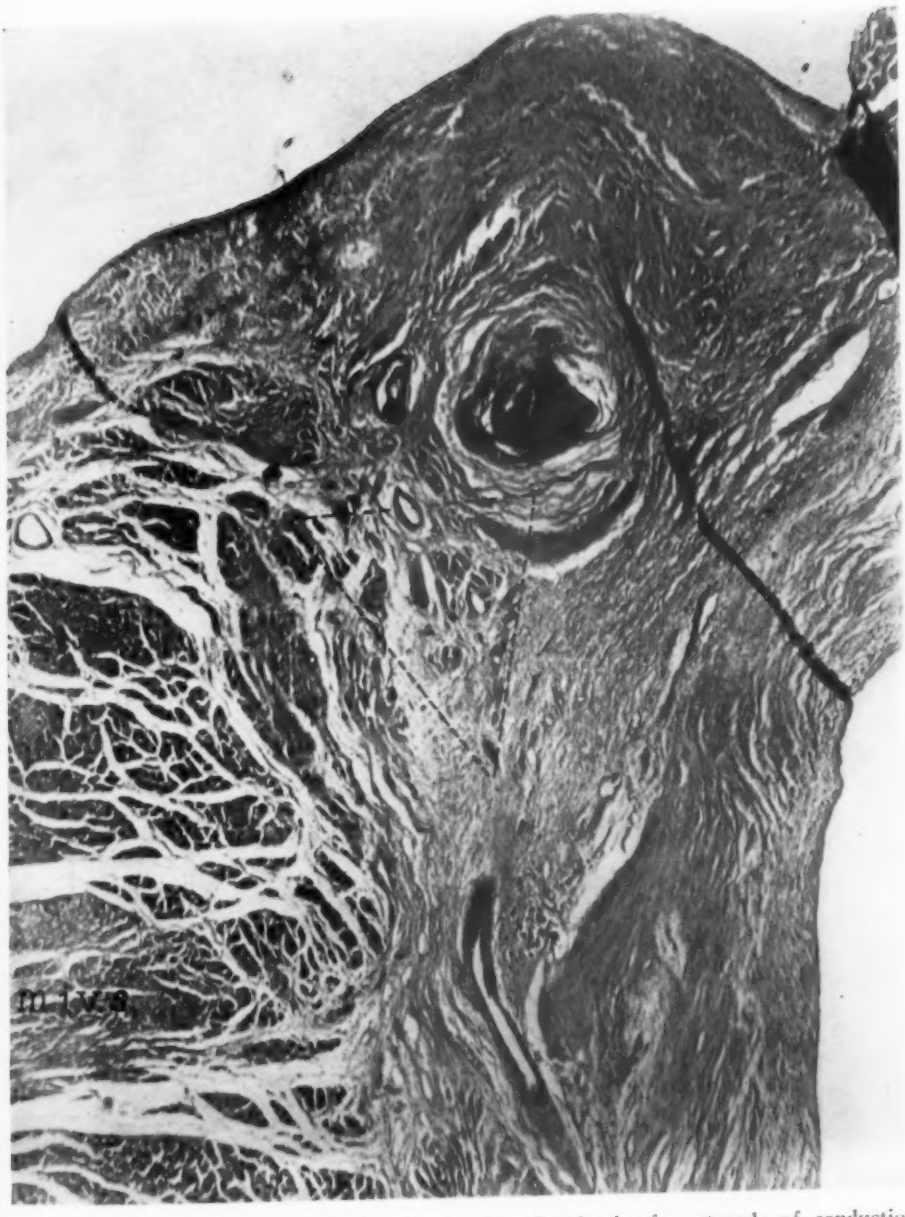

FIG. 8. Section 300, block 3, showing in the triangle the few strands of conduction tissue remaining at this point in the fibrotic bundle of His, cut transversely (×65); *m.i.v.s.*, muscular portion of the interventricular septum.

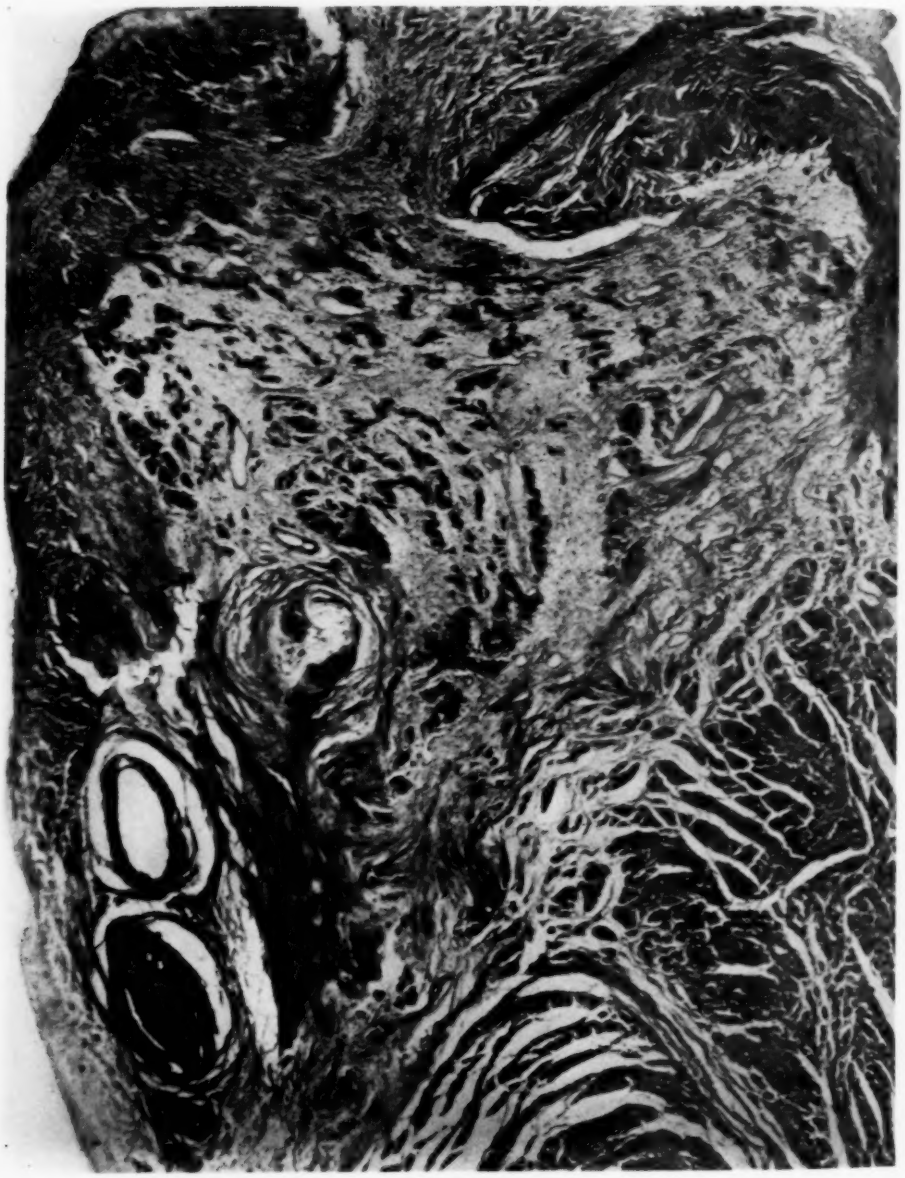

FIG. 9. Section 540, block 3, showing the bundle of His enlarged at this point but very fibrotic and appearing to be "moth-eaten," cut transversely (×65). The bundle is surrounded by denser connective tissue in the upper edge of the interventricular septum except below, where the ventricular musculature adjoins it.

the wall of the left atrium, the sclerosis of the cleft edges of the anterior leaflet of the mitral valve, the thickened chordae tendineae at the base of the cleft, and the fibrosis in the lower edge of the defect involving the bundle of His were not due to inflammatory lesions. Although we are not inclined to agree with Laubry and Pezzi [7] and other French authors that true mitral stenosis occurring in cases of interatrial septal defects is not due to valvulitis, we think that in this case the sclerotic changes enumerated above could have been due entirely to strain. During the life of the patient the cleft edges of the anterior leaflet of the mitral valve greatly overlapped. Valvulitis of such an extent would surely have resulted in greater deformity of the valve. Furthermore, had the fibrosis of the margin of the defect occurred as a result of the attack of "rheumatism," it hardly seems probable that evidence of damage of the bundle of His would have remained latent for more than 40 years. That the disturbance of conduction did not develop until the patient was more than 55 years of age is indicated by the facts that the first electrocardiograms showed only prolongation of atrioventricular conduction time and that the degree of block was progressive after this period. It appears more logical to assume that at least the fibrosis in the edge of the defect was the result of strain due to the rush of blood with each ventricular systole from the left ventricle through the interventricular portion of the defect into the right ventricle beneath the septal cusp of the tricuspid valve. The blood thus entering the right ventricle would be trapped in a little chamber between the valve and the interventricular defect because of the abnormal attachment of the free edge of the septal cusp of the tricuspid valve. The blood would swirl around in this trap and cause vibration of the edge of the interventricular defect. Such constantly recurring vibrations over a period of years might well produce fibrosis in the edge of the defect. The bundle of His lying in this edge would naturally be involved in the process of fibrosis, and the involvement would be gradual. It is possible, however, that the valvular thickening could have been due to an inflammatory lesion and the fibrosis in the edge of the defect to the entirely different factor of mechanical strain. It is true that interatrial defects seem to predispose a patient to mitral valvulitis, since the literature on this subject, reviewed by Abbott [8, 9] and by McGinn and White [10] indicates far more than the average incidence of mitral stenosis in cases of interatrial communication.

In our case the large size and overlapping of the mitral valve apparently caused obstruction to the flow of blood from the left atrium to the left ventricle. Whether this was the cause, however, of the diastolic murmur and not the passage of blood from the left atrium to the right through the interatrial defect is uncertain. The usual murmur in cases of interatrial communication is a late diastolic or early systolic murmur of varying intensity, localized in the third or fourth left interspace (Abbott [8]). In our case the diastolic murmur was heard at the usual heart rate between the ventricular beats, which were associated with a systolic murmur. The

latter was probably due to the passage of blood through the ventricular portion of the defect.

This case illustrates the tolerance of the organism to an interatrial septal defect. In cases not complicated by other serious anomalies or by mitral stenosis the patient may live to old age. Symptoms are often absent or slight. Cyanosis is rare, occurring terminally or only when there is reversal of blood flow from right to left through the opening, as when pneumonia occurs with resultant increase in intrapulmonic blood pressure (*cyanosis tardive*). In our case cyanosis was never noted. The patient did not die as a result of congestive heart failure but from ventricular standstill due to the heart block. Had this not occurred she might have lived for many years more. She was always thin and frail, a habitus probably due to the aortic hypoplasia which is present in these cases. The latter is the result of the short-circuiting of the blood from the left atrium into the right atrium. The left ventricle and the aorta fail to develop normally because of the subnormal amount of work they have to perform, whereas the right ventricle and pulmonary artery are overdeveloped for the opposite reason. It is surprising that in our case the electrocardiogram gave the picture of left ventricular preponderance instead of right, which one would expect with such an actual preponderance of the right side of the heart.

Studies of the course of the conduction system in cases of interventricular septal defect have been made by Mönckeberg,[11], Keith,[12] Wilson and Grant,[13] and Yater, Lyon and McNabb.[1] In most cases examined there was little change in the normal course of the conduction system, the special muscle bundles streaming over the edge of the defect into the ventricles. In the case of Yater, Lyon and McNabb of an infant with congenital heart block there was a large centrally located defect, and the main portion of the bundle of His was missing. Morison [14] studied the course of the conduction system in a case of persistent ostium primum. He found the atrioventricular node to be displaced posteriorly and below the coronary sinus; the fibers emerging from the node split into an abortive left branch, which ran along in the atrioventricular groove but failed to reach the left ventricle, and a large right branch which divided lower to supply both the right and left ventricles. In our case the course of the conduction system was more nearly normal, the bundle of His running along the lower edge of the defect and dividing into approximately normal right and left branches. Mönckeberg [15] examined a heart with the same defect and found the course of the conduction system to be approximately the same as in our case.

Summary

An unusual case is reported of acquired heart block dependent upon a defect of the interatrial septum, namely, persistent ostium primum. It is probably the first case of this kind ever studied completely. Heart block was due to fibrosis of the bundle of His as it ran in the very edge of the

interventricular portion of the defect. This fibrosis was probably due to strain and not to inflammation, although the patient had had "rheumatism" in childhood. The diminution in atrioventricular conductivity was progressive after the age of 57 years and was associated with numerous Adams-Stokes' syncopal attacks, in one of which death occurred. The case is apparently the third one of persistent ostium primum in which the course of the conduction system has been studied by serial sections.

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THE ANALGESIC EFFECT OF HEPATITIS AND JAUNDICE IN CHRONIC ARTHRITIS, FIBROSITIS AND SCIATIC PAIN *

By PHILIP S. HENCH, M.D., F.A.C.P., *Rochester, Minnesota*

IN THE last four years I have observed a number of patients whose pain, caused by arthritis, fibrositis or sciatica, was markedly, usually completely, relieved coincident with the appearance of intrahepatic jaundice. In two cases the jaundice apparently was not induced by any drug; in the other cases it resulted from cinchophen. However, the analgesia was not caused by the cinchophen, as will appear.

Cases of "cinchophen hepatitis" afford opportunities for studying analgesia associated with icterus, for the cinchophen is generally taken for a chronic type of pain, usually that of long standing "rheumatism." Two particularly striking examples of the effect of such jaundice have been encountered recently. Therefore, to determine the frequency and degree of relief of pain, I have reviewed all cases seen at The Mayo Clinic in which a toxic reaction has resulted from cinchophen taken for a painful condition, and concerning which adequate data are available, as well as cases of similar nature reported in the literature. The hepatitis resulting from this drug has received fairly wide attention in the last eight years,[1] but analgesia associated with jaundice resulting from it or from other hepatic disturbances has so far escaped detailed comment.

EFFECT OF JAUNDICE, UNRELATED TO DRUGS, ON THE PAIN OF ARTHRITIS

In two cases of chronic "infectious" (atrophic) arthritis, relief of pain was coincident with the appearance of a toxic intrahepatic jaundice unrelated to drugs.

CASE I

(Not Reported Before)

A physician, aged 65 years, was admitted to the clinic April 1, 1929, complaining of jaundice. From the age of 18 years he had had short attacks of "lumbago" yearly. About 1925 chronic arthritis developed in his ankles, feet, wrists and hands, and there had been considerable chronic pain, swelling and tenderness since. He received partial relief with heat, but took no medicine. Walking was particularly painful. In February 1929, he noted biliuria. March 24, jaundice, acholic stools and slight pruritus appeared; there were no chills, fever, abdominal pain, or diarrhea. He stated, "On March 25 (the day after the jaundice appeared) the pain and swelling in my joints began to diminish."

Examination at the clinic April 1, gave negative results except for jaundice,

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From the Division of Medicine, The Mayo Clinic.

graded 3, and some periarticular thickening of the involved joints, but subjectively they were negative. The liver and spleen were not palpable. There was no fever. The Wassermann test of the blood was negative. The urine contained albumin graded 2, a few casts and erythrocytes, bile graded 2, urobilin, and traces of urobilinogen. Blood counts gave normal results. Platelets numbered 192,000 in each cubic millimeter of blood. Coagulation time (Bogg's method) was eight minutes; the bleeding time was two minutes. The value for serum bilirubin was 20.3 mg. in each 100 c.c. and later it was 28 mg. (normal 1 to 1.5 mg.), and the van den Bergh reaction was direct. A cholecystogram gave negative results.

Under treatment the value for serum bilirubin dropped to 3.3 mg. and the jaundice disappeared in five weeks. In the meantime the complete relief from pain and stiffness of joints continued, and the patient was able to walk more than a mile without pain. He was dismissed from observation April 30, 1929; the diagnosis of toxic intrahepatic jaundice of unknown origin had been made.

The feet remained free from pain for about five months; the hands, for about eight months. Then active polyarthritis returned, affecting the hands, feet, shoulders, and knees. The patient returned to the clinic May 25, 1931. Motion of the shoulders and wrists was limited 50 per cent. The midphalangeal joints of the hands, the knees, and the toes were swollen and painful, graded 2. Roentgenograms of the hands and feet gave evidence of periarticular swelling, with small regions of erosion (figure 1*a* and *b*). The liver was not enlarged. Phenoltetrachlorphthalein, used for test of

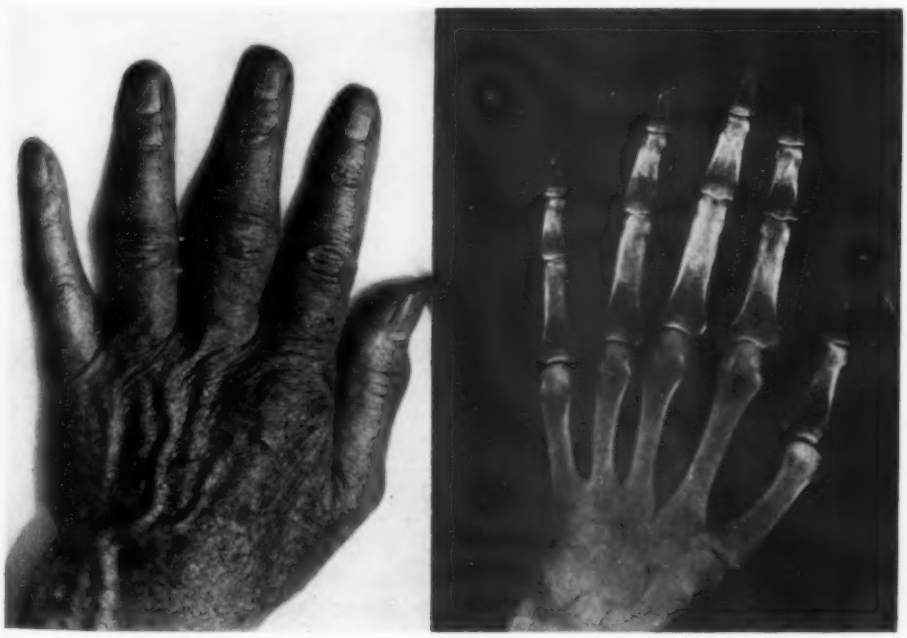

FIG. 1, *a* and *b*. Photograph and roentgenogram of hand of case 1, showing changes as seen in chronic infectious (atrophic) arthritis. (Periarticular swelling, bone atrophy, small areas of erosion.)

hepatic function, was not retained. Urinalysis and blood counts gave negative results. The value for uric acid was 2.8 mg. in each 100 c.c. of whole blood (method of Folin, 1930), that for bilirubin was 1.0 mg. in each 100 c.c. of serum, and the van den Bergh reaction was indirect.

The patient recalled that the only time he had been entirely free from pain in his joints since the onset of arthritis in 1925, was during and immediately after the episode of jaundice in 1929. Impressed with this remark I suggested a trial of bile salt or allied treatment. For 10 days he was given four tablets of decholin daily, each containing 3¾ grains (0.25 gm.) of dehydrocholic acid. No other treatment was provided for the joints. The patient noted some diuresis. During the next few days he felt much improved, stating that he could walk better than for four months, that his feet, knees and hands felt better than for a long time, and that he was able to raise the hands to the top of his head, an accomplishment impossible for three months. In spite of cloudy weather, which usually made him feel worse, his other joints remained comfortable. He refused to ascribe his relief to his relative inactivity, for he had rested completely at home for certain periods without relief. Administration of decholin was stopped, however, for the relief was sceptically ascribed to rest, to spontaneous remission, or in part to psychic factors; that it could follow the use of such a small amount of the drug seemed unlikely. The patient was dismissed from observation July 2, 1931. July 17, the generalized arthritis returned and had continued to the time of writing. He has not returned to the clinic and no further treatment with bile salts has been tried.

Case II

(Not Reported Before)

A man, aged 31 years, was admitted to the clinic March 22, 1932, on account of arthritis which had appeared in March 1931, with marked swelling and pain in the joints of the feet, the ankles, knees, hands and elbows, and, to a lesser extent, in the hips, wrists and shoulders. In October 1931, without previous medication, painless jaundice developed which lasted for six weeks. During the first two weeks of the jaundice all symptoms referable to the joints, including the swelling, disappeared; later some shifting pain returned. After the jaundice had disappeared the trouble with the joints returned and remained.

On the patient's arrival at the clinic about four months after the disappearance of the jaundice a diagnosis was made of chronic infectious (atrophic) arthritis, and apparently previous intrahepatic jaundice, cause unknown. Physical examination was negative except for the presence of considerable pain on motion of the joints. There was spindle-shaped swelling of the midphalangeal joints of the hands, and pronation of the feet was painful. The Wassermann test of the blood was negative. May 1933, the patient wrote that the arthritis was still progressively active.

Pain of Arthritis Relieved Coincident with Intrahepatic Jaundice Caused by Cinchophen

Five patients with chronic arthritis have been seen at The Mayo Clinic, whose pains apparently were definitely modified on the appearance of intrahepatic jaundice ascribed to cinchophen. The administration of cinchophen had been discontinued in each case after the appearance of jaundice. Cases of toxic reaction to cinchophen seen at the clinic have been studied from clinical, pathologic, and other aspects. Some of the cases have been reported previously, sometimes more than once, for different purposes. Indications are given in cases in which this has been done, in order that the total number of cases of toxic reaction to cinchophen seen at the clinic may not be erroneously estimated in reviews.

A detailed survey of cinchophen hepatitis has just been made by Weir and Comfort.[2] They did not consider the feature under consideration here, analgesia concomitant with jaundice, particularly in rheumatic disease. Because abstracts of cases of cinchophen hepatitis seen at the clinic were given by them, reports of these cases, as given in this paper, will include only data pertinent to my discussion. It is to be regretted that in some instances in which a serious hepatic condition commanded chief attention, details regarding the joints were not recorded, and therefore several of the cases that were included by Weir and Comfort cannot appear herein.

Case III

(Case 1 of the report by Beaver and Robertson [3] and case 15 of that by Weir and Comfort.) A man, aged 37 years, was admitted to the clinic August 1, 1929, on account of jaundice attributed to cinchophen. In December 1928, he had noted the onset of moderate pain and marked swelling of the elbows, wrists, fingers, feet and ankles. In April 1929, spindle-shaped swelling and redness of many joints of the fingers, flexion deformity of the right elbow, and considerable pain and tenderness on motion of the shoulders and feet had been present. Roentgenograms of the knees and hands had given evidence of periarticular swelling. In the three weeks preceding July 26, 1929, the man had taken about 24 tablets of atophan. July 25, jaundice, nausea, vomiting and fever had appeared. The fever endured for 48 hours only; the jaundice persisted. With the onset of the jaundice all pain and tenderness had left the joints but swelling had not been appreciably affected.

The patient died August 4, three days after his admission at the clinic. At necropsy, subacute yellow atrophy of the liver from cinchophen hepatitis, and acute tubular nephritis were found. The liver weighed 1,320 gm. (normal 1,680 gm.).

Case IV

(Case 3 of the report by Snell and Jordan,[4] case 1 of that by Weir and Jordan,[5] case 3 of that by Beaver and Robertson, and case 17 of that by Weir and Comfort.) A woman, aged 57 years, was admitted to the clinic July 8, 1929, on account of jaundice. In February, she had noted slow, progressive onset of pain, swelling and stiffness of the knees, shoulders and elbows, but particularly of the hands. Her physician had given her a few yellow capsules which had caused pruritus and which, consequently, he had stopped administering. From May until June 24 she had taken oxyliodide, on the advice of her physician, using soda baths for the pruritus, which had returned. She lost appetite and weight, and on June 26 painless jaundice and acholic stools had appeared. The patient volunteered the information that when the jaundice had appeared the pains of the joints had begun to lessen and soon had disappeared entirely. She had no pain anywhere when she arrived at the clinic. The swelling of the joints also had diminished.

In spite of vigorous treatment the jaundice increased, hepatic failure ensued and the patient died July 26, 30 days after the onset of jaundice. Complete relief of pain of the joints persisted until death. At necropsy acute yellow atrophy of the liver and acute hemorrhagic pancreatitis were found. The liver weighed 640 gm.

Case V

(Case 6 of the report by Weir and Comfort.) A woman, aged 53 years, was admitted to the clinic September 15, 1930 because of jaundice. About August 1 she had noted the onset of arthritis in the knees, elbows and fingers, with moderate pain

and stiffness. Her physician had prescribed cinchophen, of which she had taken four tablets (7½ grains or 0.48 gm. each) daily from August 15 until September 14, when jaundice appeared and the pains in the joints began to subside. The next day, at the clinic, she said that the pains in her joints were almost gone.

Examination revealed mild jaundice. The value for serum bilirubin varied between 10 and 14.9 mg. in each 100 c.c. Phenoltetrachlorphthalein was markedly retained, grade 4. The joints were subjectively negative, but some of the finger joints were slightly deformed. The woman was dismissed from observation September 29, 1930, and jaundice disappeared about two weeks later. In January 1931, she wrote that some pain had returned to one knee. In May 1933, she wrote that she felt fine and had had very little rheumatism since the jaundice.

In case 5 the arthritis was of only six weeks' duration and was characterized by pain and stiffness, but no swelling. That the jaundice in any way affected the arthritis may be questioned; it is possible that the woman was experiencing a brief episode of rheumatism which ended spontaneously. However, the patient emphasized the coincidence between the amelioration of pains in her joints and the onset of jaundice. The case therefore is included.

Case VI

(Case 7 of the report by Weir and Comfort.) A woman, aged 65 years, was admitted to the clinic January 20, 1931, on account of jaundice. For 15 years she had had marked rheumatic pains in the arms and legs, with occasional swelling of the left elbow and once of the whole arm. About November 26, 1930, she had begun to take cinchophen, 7½ grains (0.48 gm.) three times a day, consuming about 315 grains (20.5 gm.) in two weeks, when pruritus had occurred. She had stopped taking the pills, and about December 17 jaundice had appeared and had remained for 30 days. It had practically disappeared by the time she arrived at the clinic. She stated that just before the onset of the jaundice the pain in the joints had been markedly, although not completely, relieved, and that the swelling and stiffness of the joints, and the stiffness and pain of the muscles, had completely disappeared. On examination the joints were negative except for very slight creaking, and slight pain on motion of the knees.

A diagnosis of toxic cirrhosis from cinchophen, and of infectious (atrophic) and senescent (hypertrophic) arthritis was made. By January 16, 1931, the jaundice had cleared. The woman was dismissed from observation January 23. In June 1931, six months after the disappearance of the jaundice, slight pains in arms, shoulders and back were noted, but there was no recurrence of stiffness or swelling. In May 1933, she wrote that her joints were very much improved as compared to their condition prior to the jaundice.

Case VII

(Case 4 of the report by Comfort,[6] and case 10 of that by Weir and Comfort.) A man, aged 64 years, who came to the clinic May 24, 1932, had been bothered for 14 years with "chronic muscular rheumatism," and painful shoulders and elbows. In June 1930 he had been disabled by a painful swelling in one knee. For three weeks in April 1932, he had taken Cass' Rheumatism Remedy, which contains cinchophen. On May 5 vomiting had occurred and the urine had appeared dark; May 12, jaundice had appeared. He later stated that just before the onset of jaundice he had begun to note reduction of pain.

On examination the patient was jaundiced and somewhat stuporous. The liver was not palpable; the value for serum bilirubin was 25 mg. in each 100 c.c. and the van den Bergh reaction was direct. The joints and muscles were objectively negative. He recovered from the jaundice about June 20 and was dismissed June 29. About July 4, two weeks after disappearance of the jaundice, the pain had begun to return somewhat. In May 1933 his rheumatism was as severe as it had been before the jaundice.

Effect of Jaundice on the Pain of Fibrositis

The term "arthritis" implies pathologic changes involving chiefly intra-articular tissues: synovial membrane, cartilage, and articular bone. The term "fibrositis" means inflammatory hyperplasia of white fibrous tissues anywhere in the body, such as fascia, aponeurosis, sheaths of muscles and nerves, ligaments, tendons, periosteum and subcutaneous tissues. With arthritis, particularly the chronic atrophic (infectious, rheumatoid) form, there is fibrositis involving the appropriate intra-articular tissues, and there may also be more or less widespread fibrositis involving muscles and periarticular tissues. When a patient has long-continued soreness, stiffness, and pain on motion of joints, but no redness, swelling, or roentgenographic evidence of deformity, the term "chronic periarthritis" or "periarticular fibrositis" is often used to designate the clinical difference between the condition at hand and arthritis. The term "muscular rheumatism," as used in this country, is the equivalent of localized or diffuse (nonarticular) fibrositis.

The following three cases of periarticular or diffuse fibrositis demonstrated relief of pain coincident with the appearance of intrahepatic (cinchophen) jaundice.

Case VIII

(Not Reported Before)

A woman, aged 48 years, came to the clinic July 20, 1931, because of constant pains in her knees, wrists and fingers, of three years' duration. Swelling of joints had not occurred. About May 1, 1931, she had begun to take Renton's Hydrocine Tablets, which contain cinchophen. She had taken about 40 tablets prior to May 14, when painless "catarrhal jaundice" appeared and lasted for about six weeks, until July 1. With the onset of the jaundice she had experienced complete relief from all pain and stiffness. During the latter part of the period of jaundice she had had slight pain and swelling of one wrist for one day only. After the jaundice had left the pains had begun to return.

Examination revealed infected tonsils. There was pain on motion of the hips, and stiffness and creaking of the knees. Roentgenograms of hips, lumbar part of the spinal column, and pelvis, gave negative results. A diagnosis of intrahepatic jaundice from cinchophen, and chronic periarthritis, probably infectious, was made. In August 1931, the tonsils were removed. In December the periarticular stiffness and pain disappeared and they had not returned to the time of writing.

Case IX

(Not Reported Before)

A man, aged 45 years, was admitted to the clinic February 15, 1933, because of jaundice and abdominal distress. In January 1930, he had fallen on one knee, since

which time occasional pain and swelling had been noted therein. Since February 1931, he had had daily pain and stiffness in the joints and muscles of the neck, shoulders, arms and knees, but no swelling or redness. Between November 1932 and the last of January 1933, he had taken 151 Renton's Hydrocine Tablets, which relieved pain partially and temporarily. On February 1, 1933, he had noted the onset of nausea, anorexia, and dull epigastric pain. February 3, dark urine had appeared, and on February 12, jaundice. He had not had chills, fever, colic, or pruritus. Stools were light colored. With the onset of jaundice he had noted complete disappearance of all pain, stiffness and soreness of joints and muscles.

February 5, the patient was examined at the clinic. He was markedly jaundiced. The liver was just palpable. All joints were freely movable, and there was no pain on motion or on deep pressure. The Wassermann test of the blood was negative. The urine contained albumin graded 1, bile graded 2, and casts graded 2. The value for serum bilirubin was 18.8 mg. The van den Bergh reaction was direct. A cholecystogram was negative. In the hospital, light, amber-colored bile was recovered on duodenal drainage.

Under treatment, the value for serum bilirubin rose to 27.8 mg., then subsided rapidly to 5.2 mg. Several times, the van den Bergh reaction was obtained and was direct. The galactose tolerance test revealed 14.5 gm. of galactose in the urine in five hours (normal, 3 gm. or less), and later, on dismissal, 6.3 gm. A diagnosis of acute toxic hepatitis from cinchophen, and asymptomatic chronic infectious fibrositis was made. The patient was dismissed March 25, still slightly jaundiced. The jaundice was entirely gone by April 10, 1933. About two weeks later the pain and stiffness returned; they were of about the same severity as before, but remained only about four weeks, and then disappeared entirely.

Case X

(Not Reported Before)

A woman, aged 44 years, was seen at the clinic on several occasions over a period of five years, because of marked pain, stiffness and soreness. At first the right shoulder, wrist, arm and cervicothoracic portion of the spinal column had been affected; later, the hips and knees. Her disability had begun in November 1928, and had progressed steadily in spite of the usual forms of treatment. Sneezing had become painful and productive of pains radiating down the arm, from the upper part of the thoracic portion of the spinal column. The spinal column was stiff, tender, and painful on motion. Because of this pain it was difficult for the patient to turn over in bed. The right wrist had become particularly sore and tender, and for two years she had been unable to hold a glass or teapot in this hand. No redness or swelling had ever been noted, and numerous roentgenograms of the involved joints failed to give evidence of bony change. A diagnosis of progressive chronic infectious perispondylitis and periarticular fibrositis was made. Between February 15 and April 1, 1933, she took 75 Renton's Tablets. On April 1 anorexia and nausea appeared, and on April 7, biliuria and jaundice, but no pruritus.

On examination at the clinic, April 16, the patient stated that just before or after the onset of jaundice she had noted complete relief from all pain and stiffness. This relief had persisted. Marked jaundice, graded 3, was present. The liver was enlarged. There was no fever. A striking feature was that all joints, even those previously most sensitive, were objectively and subjectively normal; no pain was felt on firm pressure or on active or forced motion. Roentgenograms of the involved joints were all negative except for the shadow of one small spur between the fourth and fifth thoracic vertebrae. The Wassermann test of the blood was negative. Blood counts and urinalysis gave results that were within normal range. The value

for serum bilirubin varied between 37.5 and 28.8 mg. in each 100 c.c.; the van den Bergh reaction was direct. Galactose tolerance tests revealed an excretion of 9.2 and 7.8 gm. of reducing substance. Values for blood sugar and cholesterol were normal. Stools were at first dark; later, acholic. To determine whether the jaundice was associated with peripheral vasodilatation, the cutaneous temperatures of the extremities were determined. That of the hands and fingers varied between 31.6 and 33.5° C.; that of the toes between 27.3 and 30.2° C. These are normal temperatures. The patient's feet and hands had never been cold or clammy.

For two weeks the patient was alert and active, but in spite of vigorous treatment anorexia increased. Vomiting began April 30. The patient became drowsy. Coma hepaticum ensued, and death occurred May 7, 1933, complete analgesia having persisted to the end. At necropsy, a diagnosis of acute yellow atrophy of the liver was made. The liver weighed 865 gm. In sections of pectoral muscle taken from near the shoulder no significant pathologic change was found. All body fluids were deeply icteric; the pericardial fluid contained 8.34 mg. of bilirubin for each 100 c.c.; the peritoneal fluids, 5.17 mg. of bilirubin. The pericardial and peritoneal fluids each contained 2.0 mg. of bile salts for each 100 c.c., by a modification of the method of Gregory and Pascoe.[7] Normally none is found. Only about 2 c.c. of synovial fluid were obtained by aspiration of the knee joints; its icteric color was graded 3. Its content of bilirubin was not estimated, for it was used for culture. Special bacteriologic examinations were made to see if the jaundice had exerted an antibacterial influence and to note whether the organisms which are occasionally recovered in cases of chronic rheumatic disease were discoverable. The results were as follows: Cultures of the heart's blood and synovial fluid were negative after 21 days; culture of the spleen disclosed a green-producing streptococcus which at times appeared pleomorphic; culture of the pectoral muscle revealed a micrococcus.

Effect of Jaundice on Sciatic Pain

The effect of jaundice caused by cinchophen has been noted in two cases of sciatic pain, one associated with fibrositis, and one associated with pelvic malignancy. Although sciatica is of variable duration, depending on its cause and usually is self-limited, the pain in these two cases had persisted long enough (two years and about six months respectively) to permit the consideration that its sharp disappearance with the onset of jaundice was significant.

Case XI

(Case 3 of the report by Weir,[8] and case 14 of that by Weir and Comfort.) A man, aged 56 years, came to the clinic December 21, 1926, on account of jaundice. A rather constant right sciatic pain had appeared two years previously, accompanied by marked muscular pains in the neck. During three weeks of November he had taken 35 pills of oxyliodide. He had ceased to take these pills on account of the appearance of painless jaundice and itching. Two weeks later, edema of the legs and ascites had ensued.

On examination at the clinic, December 21, 1926, about four weeks after the onset of jaundice the patient volunteered the information that when the jaundice had appeared, the pain in the hip (sciatic area) and the pain and stiffness in the neck had completely disappeared. Moderate icterus, marked ascites, and edema of the legs, were present. The liver and spleen were not palpable. Biliuria was noted. The value for serum bilirubin was 8.3 mg. in each 100 c.c.; the van den Bergh reaction was direct. There was no tenderness or pain in muscles, joints, or sciatic regions.

Under treatment, marked improvement followed, and about January 1, 1927, the icterus disappeared. Seven years later (May 1933) the patient wrote, "After the appearance of jaundice I never had the slightest bit of rheumatism, but before the jaundice it was very bad."

Case XII

(Previously reported by Stacy and Vanzant [9]; also, case 2 of the report by Beaver and Robertson, and case 16 of that by Weir and Comfort.) A woman, aged 53 years, came to the clinic December 13, 1929, on account of jaundice of one week's duration. Seven years previously she had been given treatment with radium for an inoperable pelvic neoplasm, with excellent results. In the summer of 1929 she began to have constant pain down the back of the right thigh and leg, extending to the anterior aspect of the lower part of the leg. It was aggravated by flexion and by raising the straight leg. There was no paresthesia. She took from one to three tablets of atophan, each 7½ grains (0.48 gm.), daily for six weeks, but stopped taking them on account of nausea and vomiting. About a week later, December 7, jaundice, biliuria and acholic stools appeared, but no abdominal pain or pruritus. On her arrival at the clinic she stated that the pain of what she called her neuritis had begun to be relieved with the onset of jaundice and had since stopped entirely.

Examination revealed deep jaundice and the edge of the liver was palpable. There were no sensory changes in the legs, and no sciatic or other tenderness or pain. The Kernig sign, however, was positive on the right side. Slight infiltration of the broad ligaments was noted. The value for serum bilirubin varied between 39 and 26.5 mg. in each 100 c.c. In spite of treatment, progressive hepatic failure ensued, and the patient died December 21, 1929; relief of pain in the leg persisted thereto. Necropsy revealed acute yellow atrophy. There was also a small region of active malignant growth in the right broad ligament and ovary, which was considered responsible for the right sciatic pain.

Questionable Relief of Pain in the Presence of Jaundice Caused by Cinchophen

It happens that since I began to make these observations carefully, I have not seen a patient with jaundice from any cause who did not receive more or less complete, although perhaps temporary, relief from preëxisting rheumatic pain. However, a review of three cases of cinchophen hepatitis seen by Weir and Comfort but not seen by me, and of cases reported by others, leads to the conclusion that jaundice is not always associated with relief of pain.

Case XIII

(Case 5 of the report by Weir and Comfort, and case 4 of that by Snell and Jordan.) A man, aged 42 years, took an unstated amount of atophan and oxyliodide to relieve the pain of progressive, postgonorrheal polyarthritis of three years' duration. Jaundice ensued, and persisted for six months, at the end of which he came to the clinic, July 15, 1929. In the presence of moderate jaundice he was rather badly disabled by chronic infectious arthritis and some of his joints were tender to touch and motion. The value for serum bilirubin was only 4.6 mg., however. In July 1930, his arthritis was still troublesome. In May 1933, he was almost rid of it except in rainy weather.

Case XIV

(Case 3 of the report by Weir and Comfort.) A man, aged 52 years, had taken 360 tablets of oxyliodide in one month to relieve severe, left sacro-iliac and sciatic pain, which had followed a fall. September 29, 1930, seven months after the fall, he was admitted to the clinic. Six weeks after medication was commenced, jaundice occurred and lasted for about 30 days. When the patient was at the clinic and was slightly jaundiced, there was some pain running down the leg. The value for serum bilirubin was only 5.8 mg. in each 100 c.c. After dismissal, October 25, the man's condition improved slowly, all pain disappearing in one year.

Case XV

(Case 19 of the report by Weir and Comfort, and case 5 of that by Beaver and Robertson.) A man, aged 62 years, came to the clinic April 24, 1930. In October 1929, he had noted the onset of pain in the left arm, and for two months he had been having constant pain and stiffness of the left shoulder, arm, and hand, such that he could not raise the arm. After he had taken about 48 capsules of oxyliodide in two weeks he had begun to lose weight, appetite and strength. April 3, jaundice had appeared, but no pruritus. The patient stated that some time after he had taken the capsules the pains of the joints had been relieved somewhat.

At the time of examination at the clinic, April 24, motion of the arms and shoulders was full and free but slightly painful. The maximal value for serum bilirubin was 11.2 mg. in each 100 c.c. The patient went home, May 24, somewhat improved. The jaundice never cleared completely. Anorexia and weakness increased. In June the hands swelled again and felt stiff and painful, as did also the knees, ankles and shoulders. Because the patient was in a serious condition on his return August 2, the condition of his joints escaped description. The value for serum bilirubin reached the concentration of 16.6 mg. in each 100 c.c. Death occurred August 26.

It will be noted that in cases 13, 14 and 15, in which the degree of relief of pain is uncertain, if it was relieved at all, the rise in value for serum bilirubin was slight.

Analgesia in the Pre-Icteric Stage of Toxic Hepatitis

When analgesia has occurred it has generally arisen with, or just after, the onset of jaundice. Occasionally amelioration of pain apparently began prior to the onset of jaundice, in the stage of subclinical icterus. The following notable instance was seen, a case in which marked analgesia appeared after the onset of urticaria and exhaustion from the toxic effect of drugs, but six weeks before the appearance of icterus. Such a case would permit the hope that if any corollaries concerning treatment arise from these observations, effective concentrations of the responsible agent might be produced without the need for approaching the concentrations present at least in deep jaundice.

Case XVI

(Case 13 of the report by Weir and Comfort.) A woman, aged 60 years, was admitted to the clinic August 8, 1932, on account of jaundice. Since October 1931 she had had chronic swelling of several midphalangeal joints of the hands and marked

rheumatic pains in the arms, wrists, knees and shoulders. Between May 14 and May 24 she had taken about 200 grains (13 gm.) of farastan. May 27 urticaria had appeared and lasted for a week. Following this she had noted the onset of exhaustion, but without further medication the pain and swelling had disappeared. About July 1 nausea, loss of weight, drowsiness and extreme exhaustion had appeared. Jaundice had not ensued until about July 25, two months after she had stopped taking the drug.

On examination at the clinic, jaundice was present; the liver was just palpable. The value for serum bilirubin was 50 mg. in each 100 c.c.; the van den Bergh reaction was direct. The urine contained bile and tyrosin. All the joints were normal. By the middle of September when retention of dye was graded 2, the jaundice had practically disappeared, although there was still very slight, scleral icterus when the patient was dismissed November 1, 1932. She returned December 8, 1932, at which time one wrist was painful, and swelling had returned in one finger. In a letter, received in May 1933, she stated that she had some pain and slight swelling of her joints, but much less than she had had before the jaundice.

Effect of Toxic Hepatitis without Visible Jaundice

An inquiry as to the effect of toxic hepatitis without jaundice on pre-existing pain, if it has any effect, is also germane to the subject. Data concerning only one such case are at hand.

Case XVII

(Case 1 of the report by Weir and Comfort.) A man, aged 66 years, came to the clinic July 6, 1932. For 12 years he had had lumbago occasionally; for one year he had had constant lumbar pain, which was so aggravated by walking that he had been obliged to stop every two blocks to ease the pain. He was therefore increasing his more or less habitual dosage of cinchophen, having taken in all about 280 tablets in four years.

Examination at the clinic revealed tender lumbosacral and sacro-iliac joints, a somewhat stiffened spinal column and an enlarged liver, palpable 6 cm. below the costal margin. There was no jaundice or ascites. Phenoltetrachlorphthalein was retained to grade 3. The value for serum bilirubin was 1.8 mg. in each 100 c.c. and the van den Bergh reaction was direct. Roentgenograms gave evidence of hypertrophic arthritis of the lumbar part of the spinal column. A diagnosis of toxic cirrhosis from cinchophen and senescent (hypertrophic) arthritis with sciatic pain, was made. The patient returned November 11, 1932, because of further pain in the back; the liver was barely palpable.

In this instance at least, marked pain was unrelieved in the presence of definite toxic hepatitis without jaundice.

I saw a patient, also, about whom data are contradictory, and from whose case conclusions cannot be drawn, but the case may prevent too hasty presumptions regarding the effect of hepatitis with subclinical or slight jaundice. The patient was a man, aged 37 years, who had had progressive polyarthritis of nine years' duration, including markedly swollen fingers and early flexion deformities of the elbows. He came to the clinic October 4, 1930, and stated that about May nausea and anorexia had developed, and that he had lost 25 pounds (11.3 kg.), due to a condition which his brother, a physician, had diagnosed as poisoning from cinchophen, the result of taking

Renton's pills. The patient did not recall that he had been jaundiced, although his complexion had been sallow. He stated: "With the onset of nausea my joint pains and swelling left me entirely. After three months' illness I went south to recuperate, but soon the joints began to hurt again." On his admission at the clinic there was no jaundice; the liver was not palpable. The value for bilirubin was 1.0 mg. in each 100 c.c. of serum. There was no retention of dye. Marked chronic infectious arthritis affected many joints. The patient's brother informs me that the patient has since died, that streptococcal liver abscesses were found at necropsy, that some jaundice was present during the time when the toxic effect of cinchophen was evident, and that he recalled no particular relief of pain experienced by his brother therewith. Because the patient's statements were given voluntarily, first to a questioner who was unaware of the inquiry in which I was interested, may it not be assumed that some degree of analgesia was experienced in the presence of jaundice, and that it was of a degree insufficient to impress the patient?

Comment

Analgesia associated with hepatitis and jaundice heretofore has not received attention as far as I am aware, except for two passing comments. Case 3 of Parsons and Harding's [10] report was that of a woman who had had rheumatism of the right knee and who had taken 12 Renton's tablets. The tablets had made her dizzy but the rheumatism had disappeared. Jaundice appeared and death resulted. Grigg and Jacobsen [11] recently reported a case of subacute yellow atrophy of the liver following ingestion of cinchophen by a woman who for many years had arthritis involving the shoulders and hands. The authors commented: "It is worthy of note that after the appearance of the jaundice she had no subjective symptoms of arthritis." A few additional notations from reports of cases of poisoning from cinchophen affecting patients with rheumatism are suggestive but inconclusive (Rabinowitz,[12, 13] case 1 in both reports; Ross,[14] case 1; Winfield [15]; Reah,[16] case 3; Parsons and Harding, case 2). Notes are made regarding "absence of pain" but whether this refers to joints or not is uncertain.

In all of the cases reported in this paper intrahepatic jaundice has been present. Since beginning this study I have not had the opportunity of noting the effect of an obstructive or hemolytic type of jaundice on preexisting pain or on rheumatic disease. It should be determined whether they, too, may be associated with analgesia. In a discussion of the cases here reported, I was told by a colleague that he thought he recalled two cases of arthritis in which relief of pain was associated with icterus. In one case the icterus arose from obstructing choledocholithiasis; in the other, from a malignant process obstructing the common bile duct. Unfortunately, the patients' names could not be recalled for verification.

The agent responsible for analgesia and the mechanism whereby it acts has not yet been determined. Relief could not be ascribed to rest, for the patients were all ambulatory, for a time at least, after the onset of analgesia. Indeed many of them, free of pain for the first time in a long while, were much more active than prior to the jaundice. Cinchophen is obviously not the agent, as the cases of jaundice and analgesia without the use of any drug indicate. The dominant feature of visible jaundice suggests that a biliary constituent may be responsible. In general, in those cases in which the greatest concentration of serum bilirubin was demonstrated, the most relief was received (table 1).

The effect is probably not specific and may or may not be the result of a depressant effect of some component of jaundice on the nervous system or to a sedative action in inflamed tissues.

Therapeutic Implications

The therapeutic implications are obvious. It would be gratifying if one were able to repeat Nature's miracle, to provide at will a similar beneficence by the use of some nontoxic accompaniment of jaundice effective in available concentration. Almost everything has been advocated for rheumatism, and bile salts have been advocated for almost everything, at least by the vendors of proprietary remedies. It was probably inevitable, therefore, that bile salts already should have been included among remedies for rheumatism, but on the tenuous grounds indicated in an advertising pamphlet at hand, urging that bile salts be used therapeutically " for such conditions as rheumatism, epilepsy, asthma, infections of the gall-bladder, gall-stones, and other chronic disorders which result from autointoxication." To explore the possibilities of rational treatment, a selected group of patients is being treated with various substances (bile, bile salts, decholin, liver extracts) suggested by this study. Further discussion now is unwarranted. The interpretation of these preliminary remarks as encouragement for the indiscriminate advocacy of bile salts for rheumatic or other pain is certainly not intended and would be deplorable.

Summary

In the course of the last four years observations have been made on the effect of intercurrent intrahepatic jaundice on the chronic pain experienced by 16 patients with chronic arthritis, fibrositis, and sciatica. In two of the cases the intrahepatic jaundice apparently was not related to drugs; in 14 cases it was considered the result of toxic hepatitis caused by cinchophen. Coincident generally with the onset of jaundice, 14 of the 16 patients received partial, or more usually complete, relief of pain for variable periods; moreover, in five of the six cases in which the joints were swollen, reduction of the swelling, sometimes complete, also was noted.

TABLE I

Cases Arranged in Order of Severity of Jaundice as Shown by Concentration of Serum Bilirubin *

Case	Primary Condition	Duration	Activity, Grade	Extension, Grade	Maximal Serum Bilirubin, mg. per 100 c.c.	Approximate Duration of Jaundice	Effect
16	Chronic infectious arthritis	10 months	2	2	50.0	50 days	Complete analgesia and reduction of swelling for four months, starting after onset of toxic symptoms, but six weeks before jaundice
4	Chronic infectious arthritis	5 months	2	2	41.8	30 days, until death	Complete analgesia until death; reduction of swelling
12	Sciatica with malignancy	6 months	2		39.0	2 weeks, until death	Complete analgesia until death
10	Fibrositis	4 years	2	2	37.5	1 month, until death	Complete analgesia until death
1	Chronic infectious arthritis	4 years	2	3	28.0	5 weeks	Complete relief with reduction of swelling: of feet, 5 months; of hands, 8 months
9	Fibrositis	2 years	2	2	27.8	2 months	Complete analgesia for 10 weeks
7	Chronic infectious arthritis and fibrositis	14 years	2	2	25.0	40 days	Analgesia almost complete for eight weeks
15	Chronic infectious arthritis	2 months	2	2	11.2 16.6	20 weeks, until death	Partial relief during early stage of jaundice; probably no relief thereafter prior to death

* Cases 2, 6 and 8 are omitted, for these patients were first seen after jaundice had disappeared.

TABLE I (*Continued*)

Case	Primary Condition	Duration	Activity, Grade	Extension, Grade	Maximal Serum Bilirubin, mg. per 100 c.c.	Approximate Duration of Jaundice	Effect
5	Chronic infectious arthritis	6 weeks	2	2	14.9	4 weeks	Complete analgesia for more than four weeks; perhaps for three months
3	Chronic infectious arthritis	8 months	2	3	14.5	11 days, until death	Complete analgesia until death; no reduction of swelling
11	Sciatica with fibrositis	2 years	2		8.3 †	5 weeks	Complete analgesia; no return of pain for seven years
14	Post-traumatic arthritis and sciatica	7 months	2	1	5.8	30 days	No relief
13	Chronic infectious arthritis	3 years	2	3	4.6	6 months	No relief
17	Chronic infectious arthritis	Less than 1 year	3	2	1.8	None	No jaundice but definite hepatitis; enlarged liver; retention of dye graded 3; no relief of pain

† Patient seen during receding jaundice.

Five of the 16 patients experienced complete relief of pain which was prolonged for from two weeks to eight months, in one instance for seven years, after disappearance of the jaundice. Four patients noted complete disappearance of pain with the onset of fatal hepatitis and jaundice caused by cinchophen; the analgesia persisted until death. In one case, complete relief of pain was noted only for the duration of icterus; in another case, pain disappeared completely at first, returning slightly during the latter part of the period of jaundice. Two patients had marked, although not complete relief of pain during jaundice, and even thereafter, for two weeks and five months respectively. No amelioration of pain was experienced by two patients with slight jaundice, and one other noted some relief, which later was lost, even in the presence of definite icterus. In an additional case, that of a patient with chronic infectious arthritis and hepatitis caused by cinchophen, but without jaundice, relief of pain was not experienced.

Note. While this paper was being prepared, a case of psoriatic arthritis in which complete analgesia followed the onset of toxic jaundice unrelated to drugs was reported to me by Dr. Nathan Sidel of Boston. Following presentation of my paper at the Second Conference on Rheumatic Diseases, Milwaukee, Wisconsin, June 12, 1933, an analgesic effect on neoarsphenamine jaundice in a case of chronic atrophic arthritis was reported to me by Dr. Russell Haden of Cleveland. Dr. Sidel also reported two additional cases of analgesia in jaundice caused by cinchophen, with the observation by Dr. George Minot of Boston that in cases of coexistent pernicious anemia and arthritis, when anemia was marked and the skin tinged yellow, the arthritis was likely to be much better. With improvement in color and blood count the arthritis sometimes became distinctly worse, necessitating treatment.

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CALCIFICATION OF THE PLEURA *

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CALCIFICATION of the pleura, while not a common condition, is by no means a pathologic curiosity. The present paper is a record of 14 cases that I have seen during the past three years, and 59 that I have collected from the literature. It has seemed worth while to make a study of this condition because, being an end-result, its etiology has been disputed and obscure, its clinical significance is not well understood, and the indications for treatment are unknown. Three of the cases in my series I have operated upon for infection of the pleural cavity, and on two of them I have done a complete extirpation of the calcium deposits.

Morgagni (1682–1771) is said to have reported the first case. This is of incidental importance, for the disease is surely as old as tuberculosis and hemothorax, the two conditions which commonly cause it. Before the roentgen-ray era it was recognized only at operation or at autopsy. No uncomplicated cases were observed. Because when recognized it was always associated with empyema and because there was rarely evidence of active phthisis, it came to be generally believed that it was a result of chronic nontuberculous empyema.

With the development and more common use of the roentgen-ray, more and more cases are being recognized, while it is certainly true that the war is accountable for an actual increase in incidence. Many of the cases now being reported from Germany, France, and England are secondary to gunshot wounds of the pleura. In spite of the greater incidence and the steadily growing number of cases met with, the old conception that the condition is rarely if ever of tuberculous origin has persisted. Endres,[8] Pritchard,[23] Ulrich [27] and most others who have written extensively on the subject agree that, in the words of Pritchard, "the tubercle bacillus is rarely concerned." Deist [7] is practically the only one who has supported the opposite view. The present study tends to controvert the older and more generally accepted opinion and to support the view of Deist.

The term calcification of the pleura is a misnomer, for the calcium is deposited upon the pleura, or between the visceral and parietal layers, not in the tissues of the pleura. It is precipitated or dialyzed out of a pleural effusion, becoming encrusted upon the pleural surface much as does lime on the inside of a teakettle.

INCIDENCE

There are no satisfactory statistics on the incidence of the condition. Ulrich [27] encountered 16 cases in one year among 1845 patients examined roentgenologically for diseases of the chest.

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Sex

The sex was given in 55 of the cases analyzed in this report. Forty-seven of these were males, eight females. The preponderance of males affected with this disease is in part accounted for by the fact that it frequently follows gunshot wounds of the thorax. However, even when these are eliminated, the preponderance of males is still appreciable.

Age

The ages of the patients at the time the disease was discovered ranged between 24 years and 83 years. (Chart 1.) This shows that the condition is usually first recognized in middle and late adult life. Particularly is this

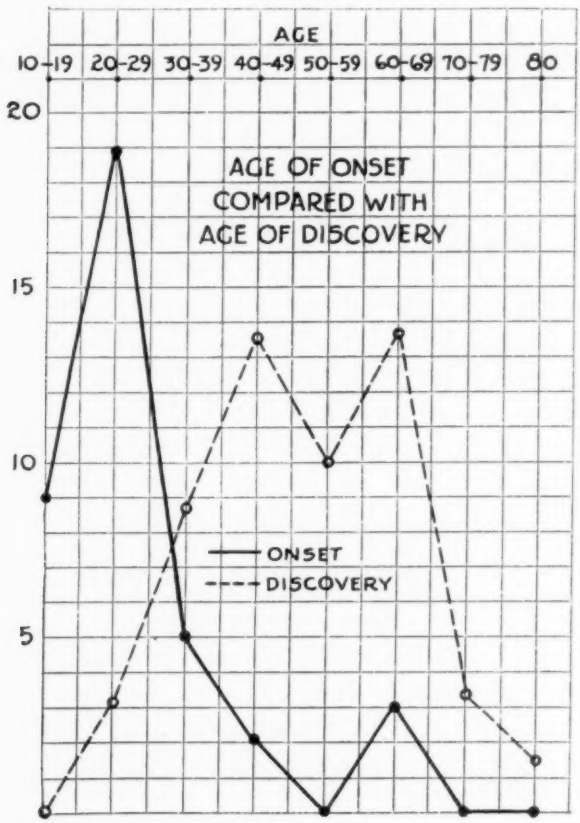

CHART 1. This chart shows the incidence by decades both for the onset and the discovery of the condition.

true of the cases not secondary to gunshot wounds. Two of the three instances in persons under 30, and eight of the 13 under 40 were secondary to gunshot wounds. It can be said, therefore, that it is rare for the non-traumatic type of the disease to be encountered in persons under 40.

In a stationary end-disease such as calcification of the pleura, the age at which the condition is discovered is of importance only when compared with the age at which it began. The age of onset is important in a consideration of the etiology; and the interval between the onset and the discovery gives valuable information as to the prognosis and the advisability of treatment.

In 37 of the cases reviewed there was a record of a past respiratory disease or injury which could be assumed to have caused the persistent lesion. In 12 there was a positive record that there had been no previous lung disease, and in 12 data on the past history were not given. The ages of onset varied between 10 and 65 years. In the following chart the ages of onset and discovery are listed by 10 year periods.

Of the 37 cases in which the ages of onset are given 27, or 73 per cent, started between the tenth and thirtieth years. The peak of 12 cases occurred in the first half of the third decade. The curve contrasts markedly with that of the ages of discovery which shows only three before the thirtieth year and which rises steadily to reach its peak in the fifth and sixth decades. From these curves one can conclude that the disease or diseases producing the condition are ones of adolescence and early life and that in most instances many years intervene between the onset and the first appearance of symptoms.

Since the etiology of those cases that follow gunshot wounds is certainly different from those that do not, and since it is the cause of the latter group that is obscure, it has seemed advisable to separate the two in a consideration of these statistics which bear on the etiology. Of the 28 on which data are available and in whom the disease was not secondary to a gunshot wound 19, or 68 per cent, began before the thirtieth year, the highest incidence being in the periods between 15 and 25 years.

Etiology

Determination of the etiology of a healed inflammatory lesion is difficult, and especially so when, as in the case of calcification of the pleura, the causative disease is often many years in the past. Opinion has been divided as to whether tuberculous or nontuberculous pleurisy was the common factor. Most have agreed that calcification could be caused by either, and it is well established that pleural hematomas frequently become calcified. Although Deist [7] has maintained that tuberculosis of the pleura was the usual etiologic factor, all of the older writers and most of those who more recently have written on the subject (Endres,[8] Pritchard,[23] Ulrich [27]) believe that the tubercle bacillus is rarely concerned. They have based their conclusions on the facts that at the time the condition is discovered clinical or autopsy examinations rarely show evidence of tuberculosis, and that the past histories of the patients often mention nontuberculous respiratory diseases, rarely tuberculosis.

Purely a priori opinion suggests that tuberculous pleurisy is the common cause. It is the condition most apt to be associated with calcification and is practically the only disease capable of producing such extensive disease of the pleura as is encountered in many of these cases without leading to either operative or spontaneous drainage or to the death of the patient. Most of the cases here discussed had never been drained. When one adds to these considerations the facts that the majority of the etiologic diseases occurred in the age periods when the incidence of tuberculosis is at its peak and that many of the patients could not remember ever having had a serious respiratory disease, the case in favor of tuberculosis seems especially strong Pneumonia and undrained empyema, practically the only other inflammatory conditions to be considered, are not likely to be forgotten.

The facts upon which those denying the tuberculous nature of the condition have based their case are open to serious question. These facts are the usual absence of clinical or autopsy evidence of tuberculosis and the absence of records of tuberculosis in the past histories. Because at the time the condition was discovered there were no signs of tuberculosis is not evidence that this was not the original disease. It is well known that the parenchymal lesion responsible for a tuberculous pleurisy is often minimal and also that a healed tuberculous lesion is indistinguishable from that of an inflammatory remnant of other etiology. Because the past history does not mention tuberculosis does not mean that tuberculosis was not present, for it is well known that even today what to the physician and the patient are pneumonia, empyema, influenza, typhoid fever, or malaria, are in fact often tuberculosis or tuberculous pleurisy with effusion.

If one sets aside 17 of the cases in which the lesion followed gunshot wounds (two of these also had pulmonary tuberculosis) and the three in which the details of the past illnesses were not given, there are left 53 cases in which the nature of the causative disease is to be considered.

Of these 53, eight had active pulmonary tuberculosis at the time the condition was discovered; three stated that at one time they had had pulmonary tuberculosis; 12 had had pleurisy with effusion, seven pleurisy; and in 13 cases there was a positive record of no previous respiratory disease. In the remaining 10 there were histories of previous respiratory disease other than tuberculosis or pleurisy. These diagnoses were as follows: influenza 1, pneumonia 1, pneumonia and empyema 3, lung trouble or chronic lung disease 4, empyema 1. Of the 13 who stated that they had had no previous respiratory disease, four reported previous illnesses which might easily have been mistaken diagnoses for pleurisy with effusion or tuberculosis. These were malaria, two cases, and typhoid fever, two cases. One of those who had had typhoid stated that she had weak lungs for two years following the attack.

An analysis of these figures shows that of the 53 cases 29 had either active or healed tuberculosis or had had pleurisy with effusion or severe pleurisy, diseases which can be assumed to be tuberculous in origin. As to

the 13 cases reporting no previous respiratory diseases one can say that probably no pleural or pulmonary disease except tuberculous pleurisy with effusion could cause such extensive residual lesions and at the same time fail to produce symptoms that would be remembered.

Of the 10 cases that reported past respiratory illnesses other than tuberculosis or pleurisy, four said that they had had chronic lung disease. It is safe to assume that these were tuberculosis. The one who had had pneumonia came under my observation. Careful questioning concerning the symptoms of this disease, which had occurred 28 years before, indicated certainly that it was not pneumonia and that it was probably pleurisy with effusion. The patient stated that he was taken sick gradually at the age of 20 with weakness, fever, and pain in his thorax and that it was three weeks before he was confined to bed or called a doctor. He continued in bed for several weeks but was weak for the remainder of the year and during this time was troubled chiefly by shortness of breath. Pneumonia and empyema, and influenza, the diseases mentioned in the remaining five cases, are diagnoses often mistakenly applied to tuberculous pleurisy with effusion. Too frequently one still sees mistakes of this kind in which, when the fluid is finally found, it is assumed to be pus and rib resection is performed.

A number of considerations seem to justify one in demanding proof that this condition of pleural calcification is ever a residuum of nontuberculous pleurisy or empyema: Tuberculosis is the disease most frequently associated with calcification; the age distribution of the cases in this series corresponds closely with that of tuberculosis; most of these cases had never had a drainage operation; moreover, in the great majority of cases it may safely be assumed that the disease was secondary to tuberculosis, while in most of the others there is a strong possibility that tuberculosis was the causative disease. One can say definitely that tuberculous pleurisy and traumatic hemothorax account for practically all cases of calcification; they are the only two conditions that have been shown positively to produce it.

Pathology

Those who have written on the subject heretofore have considered that calcification of the pleura was comparable to calcification in other tissues of the body, in other words that it was a true calcification of the tissues of the pleura. From the point of view of gross pathology the striking thing about these cases is that the calcium is found in deposits upon the surface of the pleura and is not more than loosely attached to the tissues. In one of my cases in the presence of infection the whole layer became detached en masse and lay free within the pleural cavity (figures 1 and 2) and in cases upon which I have operated it has always been easy to strip the plaques of calcium either from the surface of the visceral pleura or from between the visceral and parietal layers. It is obvious that the calcium has

been filtered or dialyzed out of a pleural exudate. In this connection the work of Andrews [1] and his coworkers on the gall-bladder is of interest. They have shown that in the presence of infection the epithelium of the

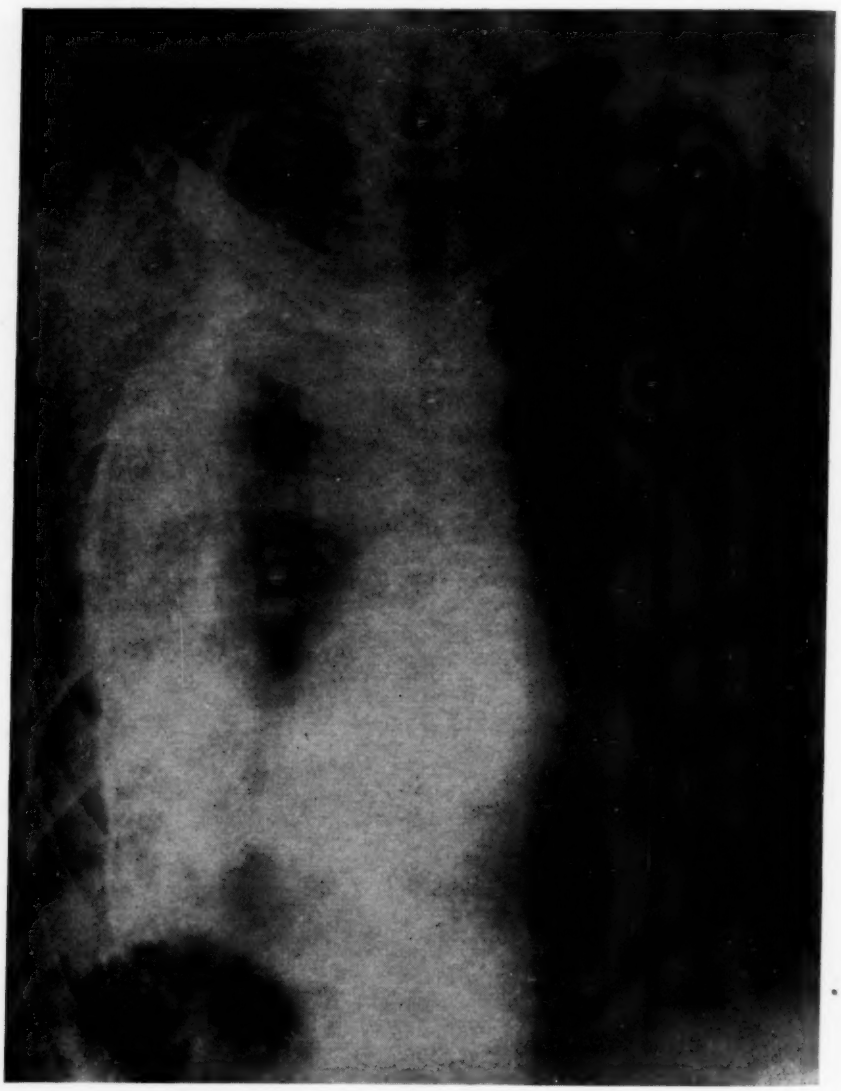

FIG. 1. Roentgenogram showing calcification of the pleura in a man 48 years old. Pleurisy with effusion occurred at the age of 20 years.

gall-bladder is frequently so altered that it acts as a dialyzing membrane and that cholesterin, instead of being absorbed as it would be under normal conditions, is dialyzed out and deposited, forming gall-stones. Pinner and Moerke [19] have also recently shown that tuberculous pleural effusions have

the same composition as the blood serum. It is reasonable to believe that under certain circumstances the pleura is so changed by infection that it becomes a dialyzing membrane and that when this happens calcium is re-

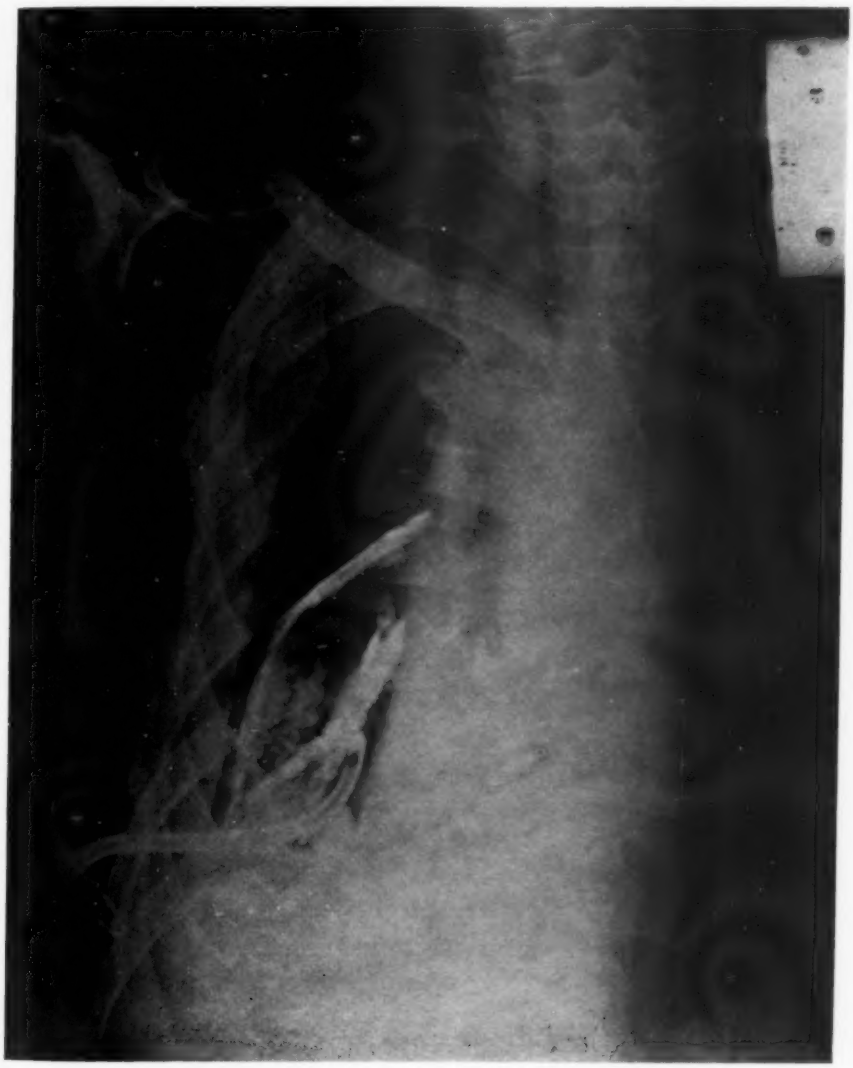

FIG. 2. Roentgenogram. A bronchial fistula developed and the pleural cavity became secondarily infected. Drainage of the pus revealed that the layer of calcium had become separated en masse and lay free in the pleural cavity.

tained as the fluid absorbs. The similarity between pleural effusions and blood serum tends to explain why hemothorax is so often similarly complicated.

The right pleura only was involved in 29 instances, the left in 32, both in five, and in seven the side involved was not designated. If only a portion of the pleura was involved it was practically always the base. In many the sheet of calcium extended uniformly from the apex to the base, a fact that argues against the possibility that the calcium was precipitated out of the exudate, for in that case it would in every instance have collected at the base of the cavity.

In most of the roentgen-rays it seemed as if the lung were partially collapsed and held in this position by the layer of calcium that encased it and in these the calcium appeared to be only on the visceral pleura. That this certainly was the condition in many of the cases was shown by findings at autopsy or operation. It is, however, impossible to say simply from the roentgen-ray findings that the lung is partially collapsed. In one of my cases it seemed certain from the roentgenograms that there was a free space between the calcified visceral pleura and the chest wall. Yet operation revealed that the layer of calcium was closely adherent to both the visceral and parietal layers leaving no free pleural space. The appearance on the roentgenogram was doubtless produced by a marked thickening of the parietal pleura. In two cases, neither of which had ever been drained, the cavity between the pleural layers was filled, in one instance with "detritus," and in the other with "thin greenish sterile pus." Mention has already been made of the case in which, following secondary infection of the cavity, the whole calcium cast of the lung became freed en masse. One of the cases upon which I operated was different from any of those I have seen or read of. A diagnosis of chronic undrained empyema was made. Aspiration gave thick greenish pus containing pneumococci. After drainage by rib resection it was noticed that what seemed to be the parietal pleura had dropped away from the chest wall around the edges of the incision. Traction upon this with a hemostat revealed that it was a partially calcified cyst-like lining to the entire empyema cavity. This came away quite easily and was pulled out much as one pulls the bladder out of a football. The groundwork of this lining membrane was composed of tough leathery greyish white material which was stratified as if it had been gradually deposited. Large portions of it were calcified.

In some of the cases secondary to gunshot wounds (none of these came to autopsy) the roentgen-ray showed, not the simple calcification of the visceral pleura, but a lung pushed away from the chest by what seemed to be large solid calcareous masses. Whether these masses were actually the large pleural rocks or calcified hematomas that they appeared to be, whether on the other hand the calcium was merely on the surface of organized blood clots or was a lining to a cavity containing air, fluid or detritus it is impossible to say from the roentgen-ray findings alone.

True bone formation in the layer of calcium has been frequently reported.

Symptoms

One would expect that there would be no symptoms in cases where there was merely calcification of the adherent pleural surfaces, and that even when the lung was partially collapsed the symptoms would be slight or absent so long as the cavity was not infected.

Concerning the symptoms, the records were complete in 53 cases. Of these only 25 had complaints directly referable to the lesion. The symptoms can be divided into two classes, those caused by the uncomplicated condition and those secondary to subsequent infection of the pleural cavity. The former were cough, pain in the thorax, and dyspnea; the latter those of chronic empyema. There were 17 cases in the first group, eight in the latter.

Of the 17 uncomplicated cases, cough was present in 11. In six it was accompanied by pain and dyspnea, in two by pain only and in three by dyspnea alone. Pain was present in 13 of the 17 cases. In six it was accompanied by cough and dyspnea, in two by cough only, in one by dyspnea only, and in two it was the only symptom. Dyspnea was present in 11 cases. In six it was accompanied by cough and pain, in three by cough alone, in one by pain only, and in one it was the only symptom.

In none of the 17 uncomplicated cases were the symptoms severe or disabling unless there was a concurrent active pulmonary tuberculosis. This was present in eight instances. In the others the cough, pain, and dyspnea were all slight.

As has already been stated, acute infection of the pleural cavity is the only serious complication that can supervene. In this series it occurred eight times. Because of the importance of this development it seems worth while to give brief summaries of these cases.

Case 11.[26] A male 59 years old fell and struck the left side of his thorax. An abscess formed in the chest wall resulting in a fistula opening into a cavity in the thorax, the walls of the cavity being covered with calcium.

Case 25.[9] A male 68 years old developed spontaneously an abscess of the chest wall which resulted in a fistula leading into a cavity in the thorax. Here again the walls of the cavity were covered with calcium. The patient could not recall having had any previous respiratory diseases.

Case 26.[25] A male 59 years old gave a history and presented symptoms in all ways similar to those of the previous case.

Case 28.[14] A female 50 years old developed fever and repeated chills. After a short time she suddenly coughed up a large quantity of pus. Autopsy showed a large empyema cavity walled with calcium. There was a bronchial fistula. The past history was not given.

Case 31.[20] This patient was operated upon for empyema at the age of 45 years. The sinus never closed. Five years later operation revealed a large chronic empyema cavity the visceral surface of which was covered with calcium. This is the type of case which has led to the assumption that tuberculosis was rarely a cause. Tuberculous empyema is common and operations for it and even for tuberculous pleurisy with effusion are performed frequently in the belief that the conditions are not tuberculous. Hence, in view of the other evidence, such cases must be considered tuberculous until it is proved conclusively that the tubercle bacillus is not and never has been present.

Case 35. This is one of the cases that came under my observation. A male 48 years old gradually developed fever, chills and weakness. About a month later he suddenly began coughing up large quantities of pus. The roentgenogram revealed the lung partially collapsed and the visceral pleura covered with calcium. A roentgenogram taken several weeks later showed that the layer of calcium had become separated from the lung en masse and now lay free in the pleural cavity. This patient had had an illness at the age of 21, the symptoms of which were consistent with pleurisy with effusion.

Case 52. This case is of particular interest in that it brings up the question whether or not the layer of calcium can become infected when there is no free pleural space and the calcium is merely interposed between the visceral and parietal layers of the pleura. If, when there is a free space in the pleura, infection can occur spontaneously, the bacteria must have reached the cavity either from the lung by direct extension or via the lymphatics, or else they must have been carried there in the blood stream. There is apparently no reason why infection could not similarly reach the layer of calcium in the absence of a free pleural space. If it did so the process would be chronic, as in the case of any infected foreign body, and would persist until the foreign body was removed. It is my belief that this was the sequence of events in the following case.

A male 36 years old gradually developed cough, fever, chills, weakness and pain in the left thorax. This pain was steady and boring in character and was severe enough to keep the patient awake at night. He had had no previous illnesses save an attack of pleurisy with effusion at the age of 10. His symptoms continued over a period of many weeks showing no signs of abating. His temperature was of a septic type and ranged between normal and 102 degrees. The roentgenogram showed that the left lung in its axillary portion was covered from apex to base with a sheet of calcium. From the appearance of the plate it seemed certain that the lung was partially collapsed and that there was a free space in the pleura. Since it was felt that his symptoms were caused by infection of the calcified pleura, several attempts were made to aspirate the cavity; this failing, an attempt was made to inject lipiodol into it. None of these was successful. Because his symptoms persisted an exploratory operation was performed. Through a high mid-axillary incision a segment of the third rib was resected. Incision through the bed of the periosteum showed that the parietal pleura was markedly thickened. The layer of calcium was exposed and a plaque of it several centimeters in diameter was resected. It peeled away from the opposing pleural surfaces without difficulty, leaving capillary bleeding. No cavity in the pleura was found, and the subsequent operations confirmed the fact that none was present and that the appearance on the roentgenogram was caused by a marked thickening of the parietal pleura. About and beneath the layer of calcium was a syrupy fluid, brownish in color and translucent. No culture of it was made. The wound was closed in layers without drainage. Healing was by first intention. Several weeks later the area of the incision became indurated in its deeper layers. This gradually extended to the surface, the wound opened and pus was discharged. A permanent sinus resulted.

There being no doubt that the layer of calcium was now surely infected, whether or not it had been before the operation, the decision was made to remove the entire cast. This was done through a mid-axillary incision in multiple stages. As soon as the area was widely opened the fever dropped to normal and has remained so since. The first operation was done 18 months ago. All of the calcium has now been removed, and the wound is clean. A relatively minor plastic operation must still be done so that healing can become complete.

Case 56. This case also is of particular interest and will be discussed in considerable detail. In many of its essential features it differed from any of the others.

It is the only one in which the history and findings suggest that calcification was secondary to nontuberculous empyema.

A male 45 years old was taken suddenly with a severe chill while at work. He was taken home and for the next two weeks was seriously ill. He improved gradually but his fever remained elevated. He had sweats and did not regain his strength. Finally he was sent to the Cook County Tuberculosis Hospital with a diagnosis of pulmonary tuberculosis. The physical and roentgen-ray examinations showed signs of fluid at the base and in the axillary portion of the right pleural cavity. Aspiration gave thick greenish pus which on smear and culture showed pneumococci. The findings and the operative procedure in this case have already been described under the section on pathology. The bladder-like calcified lining to the cavity was removed, the pus having first been taken out, and wide open drainage was established. The cavity gradually became obliterated and the sinus closed.

Everything suggests that this was an instance in which the condition followed ordinary pneumococcic empyema. In this connection it is important to note that the pathology was definitely different from that recorded in any of the other cases. This may have been because the case was early or because it was of different etiology. Because pneumococci were found does not mean that tubercle bacilli would not have been found had they been looked for. Secondary infection of a tuberculous empyema is not uncommon. It should be noted that the patient was a sand molder and that he had definite pneumoconiosis, a condition which predisposes particularly to tuberculosis.

Physical Signs

The physical signs are those of thickened pleura, i.e. dullness and decreased to absent fremitus and breath and voice sounds. The most striking finding in cases where the calcification is at all extensive is a marked retraction and immobility of the affected side.

Treatment

The chief value of this study is the information it affords regarding prophylaxis. Traumatic hemothorax and serothorax should be observed carefully and aspirated if absorption is not rapid. It has been the practice in regard to tuberculous pleurisy with effusion to consider it of therapeutic value and to aspirate only to relieve dyspnea. The cases here reviewed show that there is some danger that the lung will remain permanently collapsed, the visceral pleura becoming calcified. They indicate that all cases should be carefully followed until absorption is complete or until it becomes evident that aspiration will be necessary. Replacement of the fluid by air would probably tend to decrease the incidence of the complication, but I do not feel that simple pleurisy with effusion warrants a prolonged pneumothorax unless it can be demonstrated that the lung is seriously involved.

The statistics given in chart 1 indicate that the condition is not inconsistent with long and active life. In the uncomplicated cases either there are no symptoms or those that are present are slight. Certainly in these cases no treatment is indicated. The danger of subsequent infection of the pleura is much less than that incident to any operation which might remove it.

Once the calcium layer has become infected the treatment is the same as that of chronic empyema save that all of the calcium must be removed. Unless this is done, it will act as a foreign body and prevent complete

healing. A combination of the Schede and DeLorme operations is indicated, although often where the deposits are on the visceral pleura only, the plaques can be pulled off without performing a true decortication.

Summary

From the study of the cases in this series the clinical picture of calcification of the pleura can be summarized as follows: The acute symptoms of tuberculous pleurisy with effusion or of traumatic hemothorax abate without complete absorption of the pleural fluid. As this subsequently is slowly absorbed, the calcium in it is dialyzed out and deposited on the pleural surface. This encrusting of the surface of the lung may take place before this organ is completely reëxpanded, in which case its partial collapse is made permanent by the rigid mold enclosing it. In other cases the lung fully reëxpands and the calcium is left as a layer interposed between the visceral and parietal layers of the pleura. In many instances there are no symptoms referable to this condition. In others there are pain, cough, or dyspnea or all of these symptoms and a marked immobility and retraction of the affected hemothorax. The only serious complication which can develop is infection of the pleural cavity or, when there is no free space, of the layer of calcium between the opposed pleural surfaces. This accident may supervene at any time subsequent to the establishment of the condition. In these cases drainage results in a chronic empyema which necessitates an extensive thoracoplasty and removal of all of the layer of calcium.

Conclusions

1. Calcification of the pleura is an uncommon but not a rare condition.

2. It is the end-result of the delayed and faulty absorption of tuberculous pleurisy with effusion or of traumatic hemothorax. An occasional instance may be secondary to nontuberculous empyema, but this has not been definitely proved.

3. Most patients afflicted with calcification of the pleura have few or slight symptoms and the condition is not inconsistent with long and active life.

4. In a certain number of cases the pleural cavity or the layer of calcium between the two pleural surfaces becomes infected, and if this occurs the calcium acts as a foreign body and maintains a chronic infection until whatever cavity may be present is completely obliterated and all of the calcium is removed.

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"ALLERGIC" SHOCK

III. FROM SUBSTANCES OTHER THAN POLLEN AND SERUM*

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IN AN atopic individual the administration of an overdose of an antigen to which he is sensitive gives rise to a peculiar syndrome which is characterized by more or less generalized edema, urticaria, wheezing, nasal and conjunctival swelling, vomiting, diarrhea, bladder and uterine symptoms and occasionally convulsions. In fact, any known symptoms of allergy may occur. Usually there is a combination of respiratory and dermal edema. The severity of the symptoms is proportionate to the degree of sensitivity of the patient, the size of the overdose and the rate of absorption. These reactions are most frequently encountered following therapeutic injections with serums (1) and pollens (2) or following intradermal skin testing. But it is general knowledge that the same syndrome not infrequently occurs without injections, for instance following contact with a certain food or animal, particularly in children, or in cases of cold and heat sensitivity following sudden chilling or overheating.

In spite of the relative frequency of these incidents they have received very little attention in the literature. Some have called them human anaphylaxis because of their resemblance to anaphylactic shock in the lower animals. Others prefer to limit the term anaphylactic shock strictly to the phenomenon observed in the animal experiment. The latter school states (Coca [3]) that muscle-spasm-producing antibodies which are characteristic of animal anaphylaxis are not found in men, while a different type of antibodies so-called "reagins" are said to be present in allergic shock in men. The experimental work of Ratner et al.[4] is probably the most important argument against such a strict separation of anaphylactic and allergic shock. In addition it has been observed that shortly after shock in men no reagins are present in the blood (Walzer,[5] Waldbott [6]). Because of the clinical and pathogenetic resemblance of this phenomenon in man to that seen in the sensitized animal on the one hand, and because of the uncertainty (Cooke and Spain [7]) of our knowledge regarding anaphylactic antibodies on the other hand, it appears to me more appropriate to designate the above mentioned phenomenon anaphylactic shock. However in order to avoid confusion, I shall refrain from using this term at present.†

I have elsewhere [8] presented evidence that what has been called "thymic death" is closely related to, if not identical with this phenomenon: In 34 cases of so-called "thymic" death which were selected from a group of 102 cases thus diagnosed by various pathologists and in which no apparent

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† The controversy regarding the nomenclature, whatever the final consensus may be, does not justify, I believe, the neglect of this important subject, as has actually been the case during recent years.

cause of death had been determined, pathological changes were found which could be considered characteristic of " allergic " shock. In a follow-up study (Waldbott and Anthony [9]) of 30 children who had previously been diagnosed by the roentgen-ray method as cases of thymic hyperplasia, 24 were found to be definitely allergic; in four of the remaining six, this diagnosis was suggestive but not definite.

The following three facts form the principle obstacles to such an explanation of so-called " thymic death ": 1. Human anaphylaxis is not recognized at present as a clinical entity; in fact it is said by some not to exist. 2. Anaphylactic shock is not generally believed to occur by ways other than by injections. 3. " Thymic " death occurs after absorption of non-protein substances, for instance, following the administration of local and general anesthetics which have heretofore not been held responsible for the production of anaphylactic symptoms.

The last objection cannot stand any longer, since Landsteiner et al.[10] and Avery et al.[11] have demonstrated experimentally that antigenic qualities do not depend on whether or not a substance contains protein. Waldbott [8] has shown that local and general anesthetics, the administration of which has often been followed by " thymic " death, may give rise to atopic symptoms.

In order to aid in the recognition of the above mentioned syndrome as a clinical disease entity I studied reactions after the administration of pollen and eight cases of death following serum injections. The present study is concerned with shock following injection of substances other than pollen and serum. I have collected from various hospitals and physicians a series of 26 cases which manifested " reactions " following absorption of such antigens. Eight of these cases, which are here reported, showed the characteristic manifestations of " allergic " shock. Three occurred following non-protein antigen, or following dermal absorption without an injection; in one the reaction can be attributed to an accidental intravenous injection in a patient who tolerated previous injections of the same antigen; and three cases were so-called " atypical reactions " as previously described following injections of pollen extract.

Differential Diagnosis

Before enlarging upon these cases I wish to mention briefly some of the conditions which were encountered among the 19 remaining cases, since the lack of a clinical differentiation of " allergic " shock from similar reactions has often been the source of widespread confusion. Most of these reactions have no association with hypersensitiveness whatsoever.

(*a*) *Reactions Due to Thrombosis.* There are accidents which occur due to the formation of thrombi. These usually become lodged in the lungs, producing the clinical symptoms of pulmonary embolism. The patients develop a sudden severe pain in the chest, cough and expectoration imme-

diately after an injection. Upon physical and roentgen-ray examination an area of consolidation is usually found. The clinical course is somewhat similar to bronchial pneumonia and, if not fatal, the patient improves after one to two weeks. Three such cases were encountered, one after an injection of 0.6 gram of neoarsphenamine, two after intravenous injections of highly concentrated glucose. It is possible that what has been described by Hanzlick and Karsner [12] as anaphylactoid shock in the animal, characterized by pulmonary thrombosis, is identical with the phenomenon just mentioned. Some (Brines [13]) have described similar reactions after blood transfusions and associated them with the incompatibility of blood groups.

(*b*) *Febrile Reactions.* In two cases shortly after the injections of glucose, chills, high temperature and collapse developed with lethal exitus within a few hours. Such reactions may be brought on by certain chemicals, by bacterial contamination or by other protein elements which may have been present in the solutions. What is called speed shock by Hirshfeld et al.[14] is probably due to similar causes.

(*c*) *Focal Reactions.* It has been noted (Hench [15]) that an injection with any antigen is apt to activate a dormant infection such as chronic appendicitis, furuncle, a tooth abscess, heretofore quiescent and thus account for a rise in temperature. In two cases following pollen injections I observed the flare-up of a furuncle which had been practically healed. But in this series no such instances of focal reactions were encountered.

(*d*) *Toxic Reactions.* There were two cases in which the manifestations of the reactions can be well explained by the pharmacological or toxic effect of the drug administered. For instance in a patient who received a sclerosing intravenous injection of quinine urethane the immediate occurrence of ringing in the ears, abdominal pain and menorrhea which lasted for one hour was attributed to the pharmacological effect of quinine. In one patient (table 2) who died within a few minutes after the injection of novocaine which probably was given intravenously by accident, the symptoms and pathological findings pointed to novocaine intoxication.

(*e*) *Syncopal Reactions.* Another type of "reaction" after injection, of which one should be aware, is the ordinary fainting spell usually characterized by pallor and a slow pulse.

(*f*) *Serum Sickness.* Probably the most frequent source of confusion is the lack of a distinction between "allergic" shock, especially the delayed type, and serum sickness. In both conditions there is the common symptom of urticaria and both are associated with hypersensitiveness. But the mechanism and immunological significance underlying serum disease appear to differ entirely from those connected with "allergic" shock. I attempted to illustrate some of the distinguishing features in table 1.

Report of Cases

The literature contains very few references to "allergic" shock from substances other than pollen and serum. Cooke [16] encountered a fatal case

TABLE I

Distinction between "Allergic" Shock and Serum Sickness

	Occurs in	Incubation Time	Symptoms	Epinephrin	Results
"Allergic" Shock	Only sensitized individuals	Immediate (intravenous injection); otherwise a few minutes to 24 hours	*Only allergic Urticaria* Sneezing Coughing Wheezing Vomiting Diarrhea Convulsions, etc.	Definite response	Temporary relief of previous sensitization
Serum Sickness	Sensitive and nonsensitive	3 to 12 days	*Urticaria* and Simulating Acute *Infections* Fever Joint swelling Glandular enlargement	May relieve urticaria, otherwise ineffective	More sensitive (?)

following an intradermal skin test with Le Page's glue; Baagoe [17] following the injection of egg white; von Starck [18] following ingestion of peas; Maytum and Magath [19] recorded recently a severe nonfatal reaction after an injection of gum acacia. On the other hand the serum sickness type of reaction is not uncommon following administration of nonprotein antigens.

1. Nonprotein Antigen

I was not able to find any description of true "allergic" shock due to a nonprotein antigen. Stokes [20] noted that symptoms which can be considered characteristic of this syndrome occasionally occur following injections of sodium iodide. Curtis [21] reported a case of sudden death following an injection of bismuth tartrate in which the time interval of four weeks, which separated the fatal injection from the last previous one, may have accounted for the fact that an injection, previously harmless, produced death. Among the many reports of "reactions" following injections of arsphenamine (Stuart [22]) very few are recorded which resemble the true anaphylactic type.

The following are two instances of "allergic" shock from nonprotein substances.

CASE I

J. L., 45 years old, was given an injection of 0.5 c.c. quinine hydrochloride and urethane on August 29, 1930, to produce sclerosis of varicose veins. At that time he complained of a slight fullness of the throat which quickly subsided. On September 4, 1 c.c. of the same drug was given without ill effect. The third injection of 2 c.c. on September 11, produced a slight choking sensation, headaches, and a rapid pulse. After an interval of one month (October 10) 0.5 c.c. was administered into the lesser saphenous vein, a tourniquet having been previously applied above the site of injection. Within three minutes he again complained of fullness of the throat and began to sneeze. Marked swelling of the lips, tongue, face and ears developed and considerable dyspnea and cyanosis occurred. The edema rapidly became general; the patient be-

came pulseless and unconscious. After several minutes following the use of epinephrin, oxygen and artificial respiration, he regained consciousness and vomited. For the subsequent two or three days the patient complained of general weakness, pain in the abdomen, muscle soreness and headaches.

Comment. In this case the injection of a combination of two simple chemical substances produced the identical train of clinical manifestations which we see in reactions following pollen injections. It is noteworthy that after the lapse of four weeks, one-quarter of the dose of the previous injection produced very severe symptoms while the previous injection had caused very little discomfort. This suggests, as in the case of Maytum and Magath, that the degree of sensitivity may become enhanced as the result of the lapse of a certain time between injections.

CASE II

Mrs. L. S., 44 years old, an asthmatic sensitive to various foods, to pollen and to a fungus identified by Dr. C. P. Stapleton, University Hospital, Ann Arbor, as *Monilia parapsilosis*, had responded well to the oral administration of a saturated solution of potassium iodide. While she was being given an intravenous injection of about 0.25 c.c. of a 10 per cent solution of sodium iodide, a very severe coughing spell, sneezing, dyspnea, marked cyanosis, and some edema of the skin developed. One-half c.c. of epinephrin was administered immediately and repeated after two minutes. The shock symptoms were controlled within a short time. Aside from some urticaria and general malaise the patient had no further untoward symptoms. The asthma which had been present up to this time was relieved for several weeks. Skin tests showed a slight erythema following local application of potassium iodide, but a negative reaction to sodium iodide. Passive transfer tests were negative for both salts.

Comment. In this case the patient was apparently extremely sensitive to sodium iodide but not to the potassium salt of the drug. Furthermore, the temporary relief of asthma following the "allergic" shock should be stressed as it is in line with our experience in shock from pollen injections

2. Absorption of Antigen from Skin

The following represents a case of typical "allergic" shock without an injection.

CASE III

B. T., 2 years old, showed rather marked reactions to certain foods, ragweed, etc. Immediately after application of powdered walnut material for skin testing by the scratch method a large wheal was noted which spread within one minute over the whole back and gave rise within three minutes to generalized urticaria associated with wheezing. One-half c.c. of epinephrin controlled this reaction. The child had been breast fed and the mother assured me that the patient had never had occasion to come in contact with food containing walnut. The child had a roentgenographically enlarged thymus.

Comment. So far as could be determined the child had never eaten the food to which she was sensitive, a fact which is well in accord with the

present conception of transmission of reagins through the breast milk and through the placenta.

The production of an " allergic " reaction through absorption from the excoriated skin is noteworthy. This brings up the question whether or not such reactions can be brought on by absorption from other channels such as the respiratory and intestinal tracts.

3. Accidental Intravenous Injection

That with pollen injections there is danger of accidental intravenous injections or of back seepage of extract into a punctured vein has been stressed before. The following case is an instance in which an accidentally intravenous injection accounted for the production of " allergic " shock in an individual in whom previous injections had been harmless.

CASE IV

Mrs. B. J., 25 years old, was given a series of injections of sterile milk intragluteally for pelvic inflammatory disease. She had received 5 c.c. at a dose at intervals of three to 10 days. When the same amount was again administered after 10 days she developed, within one minute after the injection, dyspnea, cyanosis, sneezing, edema of the lips and face and generalized urticaria. This was soon controlled by an injection of 0.75 c.c. of epinephrin and left no noticeable after effect.

Comment. That we are dealing here with a true " allergic " reaction is indicated by the simultaneous occurrence of dyspnea and dermal edema. Since the patient had tolerated previous injections of milk, it can be supposed that she may have become artificially sensitized by the previous injections. The suddenness of the reaction and the absence of a local swelling at the site of injection suggest that the milk must have been given intravenously or that a vein must have been punctured and back seepage of the milk into the blood stream have occurred.

4. Atypical Reactions

As previously stated, the symptoms of " allergic " shock are usually very uniform and well known to those working with pollen extracts. In certain instances, however, there is a predilective involvement of certain organs by the allergic edema. These reactions I have previously termed " atypical reactions." The following are some of the factors which may give rise to their occurrence:

(*a*) *Site of Injection.* Róth and Szauter [23] have demonstrated experimentally that the manifestations of shock are subject to great variability depending upon the site of injection of the antigen. If the antigen is introduced into the venous system, the capillary circulation of the lungs, which is then first reached by the antigen, becomes principally involved by the allergic reaction and there is clinical evidence of wheezing and dyspnea. Since absorption of subcutaneous injections takes place largely through the

lymph and venous systems, the predominance of pulmonary symptoms in anaphylaxis is readily understandable. The investigations of Róth and Szauter also showed that if the injection is given into the carotid artery, the edema occurs in the brain, and convulsions and other cerebral symptoms manifest themselves. If the injection is made into the portal vein, the clinical syndrome of collapse with disturbance of the liver function is most pronounced.

(*b*) *Previous Allergic Focus.* In addition, the symptomatology of "allergic" shock may become modified if a previous allergic lesion is present (Waldbott [2]). Those organs which have previously been the seat of an allergic manifestation, such as the lungs, the skin, or the gastrointestinal tract, will be more readily affected than other parts of the system. The following are typical examples produced by antigens other than pollen and serum.

Case V

M. D., a six month old boy, had been a sufferer from eczema, being sensitive to rye, wool, milk, wheat, etc. Since dietary measures were unsuccessful he was given injections of extracts of milk, wool, and rye. Within 10 minutes after the first administration of a rye extract (1/20 c.c. of a dilution 1:100) a severe generalized urticaria and a marked swelling of the area of injection ensued. No wheezing or swelling of the mucous membranes was present. For six hours the child had to be given small amounts of epinephrin at intervals of 15 to 30 minutes in order to control the reaction. There was no further ill effect. After two days a marked improvement in the eczema was noted. Skin tests for rye, wool, and wheat were negative for three weeks but became positive again after this interval. On the eighth day a blood specimen was obtained for passive transfer. No reagins for rye, wool, or wheat were found.

Comment. The "shock organ" in this case was the skin. The fact that after the shock no reagins were present is noteworthy in view of our general observation of temporary improvement of an existing allergic condition after the occurrence of shock.

Case VI

Mrs. R. N., aged 26, had migraine headaches about every six months and showed marked skin reactions to various foods, chicken feathers and wool. In an attempt to desensitize the patient, after several previous injections an accidental intravenous injection of feather extract must have been given. Within 10 seconds a typical attack of migraine headache occurred. It seemed to respond promptly to 0.33 c.c. of epinephrin. During the attack, the patient experienced numbness in the right arm, vomiting, and noticed cloudy spots in the right eye, symptoms which had often before been associated with seizures of migraine.

Comment. Insofar as I can determine, the literature does not mention the occurrence of an attack of migraine headache as a reaction brought on by the injection of the antigen determined by skin tests and promptly controlled by epinephrin.

(*c*) *Tissue Specificity of Antigen.* The capacity of certain antigens to combine selectively with certain tissues is another factor which tends to modify the symptoms of " allergic " shock. It is known, for instance, that arsphenamine attacks the liver and the brain more readily than other tissues; cocaine has an affinity for the nervous tissues. Two cases of procaine death have been observed in which convulsions were the outstanding symptoms. In one (case 7 in table 2) the autopsy revealed evidence of anaphylactic shock while the autopsy findings in the other case suggested procaine intoxication due to the sudden effect of an accidentally intravenous injection in a debilitated individual.

Reactions from bacterial antigens show a somewhat different course from those of other antigens. In two such instances the symptoms of chills and fever were encountered in addition to the presence of urticaria, wheezing, and dyspnea. The following case is an example.

Case VIII

Dr. B. W. L., a sufferer from migraine headaches, who was sensitive to various foods, administered to himself 1 c.c. of one of the commercial respiratory vaccines on account of a " cold " in his nose and chest. Within a few seconds after the injection he developed severe urticaria, dyspnea, abdominal pains and dizziness. Thirty minutes later a severe chill developed which was followed by temperature ranging between 103 and 104 degrees. The urticaria and dyspnea were relieved by a 0.75 gr. capsule of ephedrine sulphate. Extreme weakness, numbness in his fingers and a low blood pressure persisted for several days.

Discussion

In comparing these reactions, and those following pollen and serum injections, with the anaphylactic experiment in animals, very little difference can be detected as far as their clinical course is concerned. The shock apparently represents a defense mechanism of the system against a sudden invasion of any antigen to which sensitiveness exists. The patients later appear to be distinctly improved and in a " hyposensitive " state, although usually only for a short time, presenting thus a similarity to the anti-anaphylactic state which occurs in the animal after the reaction.

While in most cases the sensitivity is not acquired, case 1 illustrates that the tendency toward shock may be either acquired or at least greatly enhanced. The time interval between injections, the size of the shocking dose, the individual degree of sensitivity, and the mode of absorption (intravenous) are the determining factors in the production of shock. In this respect again, there is a close parallelism between human and animal shock.

Summary

1. Seven cases of " allergic " shock from substances other than pollen and serum are reported. Three occurred after injections of nonprotein substances (quinine hydrochloride and urethane, sodium iodide, and novo-

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While in most cases the sensitivity is not acquired, case 1 illustrates that the tendency toward shock may be either acquired or at least greatly enhanced. The time interval between injections, the size of the shocking dose, the individual degree of sensitivity, and the mode of absorption (intravenous) are the determining factors in the production of shock. In this respect again, there is a close parallelism between human and animal shock.

Summary

1. Seven cases of "allergic" shock from substances other than pollen and serum are reported. Three occurred after injections of nonprotein substances (quinine hydrochloride and urethane, sodium iodide, and novo-

TABLE II

Clinical and Autopsy Data in Two Cases of Death Following Novocaine Injections

Initials, Sex, Age, Purpose of Anesthesia	Dose	Allergic History	Onset of Symptoms Following Beginning of Anesthesia	Death	Symptoms	Local Reactions	Lungs	Lymph Tissue	Tissue Eosinophilia	Other Findings
P.R.D.* male, 21, tonsillectomy	Not stated	*Chronic nasal catarrh;* 3 previous operations	10 to 15 minutes	7 min.	*Dyspnea* Convulsions	Marked *edema in pharynx and larynx (Eosinophiles)*	Marked *alveolar edema; emphysema; atelectasis*	*Thymus 29 gm.; hyperplasia of intestinal mediastinal glands;* lingual tonsil	*Yes*	Congestion of cerebral and meningeal vessels. Intense congestion of liver. *Adrenals hypoplastic*
A.J., female,† 26, pneumothorax for tuberculosis	1 c.c. of 2% sol.	None	Immediately	30 min.	Spasticity of neck; dilatation of pupils; convulsions	None	Advanced tuberculosis	Not enlarged	No	Edema of meninges. Congestion of liver

* Courtesy Dr. C. V. Weller, University Hospital, Ann Arbor, Mich.
† Courtesy Dr. J. A. Kasper, Herman Kiefer Hospital, Detroit. Evidence suggesting anaphylactic shock in italics.

caine); one during a skin test for walnut by the dermal method; one as a result of an accidental intravenous injection of milk; and one following an injection of vaccine. There were two cases of "atypical" reactions similar to those following injections of pollen extracts in which injections of extracts of rye and chicken feathers produced flare-ups of previous allergic lesions.

2. The above cases of shock were selected from a series of 26 "reactions." Among the remaining 19 the reactions were due to pulmonary thrombosis, to toxicity of the drug administered, or they represented febrile reactions, focal reactions and those of serum disease. Confusion of such "reactions" with "allergic" shock should be avoided. The pathological findings in a case of shock from novocaine are contrasted with those in a case of sudden death following a novocaine injection probably due to novocaine intoxication.

3. Comparing the reactions of the eight cases with the data previously reported on shock following injections of pollen and serum, no essential difference in the mechanism or the clinical course can be detected. An exception is perhaps that the affinity of certain antigens for certain tissues may alter somewhat the symptomatology of shock.

4. It is felt that human "allergic" shock represents a definite clinical entity, the recognition of which is of particular importance in the explanation of sudden death of unknown origin. Edema in various parts of the body, particularly in skin and respiratory mucous membranes, is its chief pathological characteristic.

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REPORT OF TWO UNUSUAL CASES OF PRIMARY CARCINOMA: I. PRIMARY CARCINOMA IN THE LIVER, WITH CIRRHOSIS OF THE LIVER, OCCURRING IN A FEMALE. II. PRIMARY CARCINOMA IN THE JEJUNUM *

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Primary carcinomas in the liver and in the small intestines, especially in the jejunum, are sufficiently rare to be reported. This is especially true when some unusual features accompany the conditions.

Up to about 1871, primary carcinoma in the liver was reported quite frequently, but since then, due to the more thorough examinations and the more careful observations at autopsy, many of such cases are found to be secondary to carcinoma in other organs of the body. In 36 years, from 1870 to 1906, about 18,500 autopsies were performed at Guy's Hospital, London. Among these, only 24 cases of undoubted primary carcinoma in the liver were found, giving an incidence of 0.13 per cent of all deaths at that hospital.[1]

Winternitz [2] found three cases among 3,700 autopsies, or an incidence of 0.028 per cent. Eggel [3] collected 163 cases of primary carcinoma of the liver and reported an incidence of 0.05 per cent of this condition in the total number of autopsies. Counseller and McIndoe [4] report five cases of primary carcinoma in the liver in 5,976 necropsies, an incidence of 0.08 per cent.

Primary carcinoma of the liver is a disease of middle life, the average age being about 52 years. Hedinger [5] reports the curious fact of the occurrence of primary carcinoma of the liver in two sisters, 71 and 77 years of age, respectively, who died within one week of each other. Kaufman reports one case in a child 15 years of age; and Kilfoy and Terry report a case in a child nine years of age. Wallstein and Mixsell report a case of primary carcinoma of the liver in a child nine months of age. In contradistinction to carcinoma of the gall-bladder, which is more frequent in females, primary carcinoma of the liver is more frequent in males.

In the past two decades, our conception of primary carcinoma of the liver has materially changed. We know now that the majority of these cases are associated with cirrhosis of the liver. Counseller and McIndoe state that this association is present in about 70 to 80 per cent of the cases. Strong and Pitts [6] report nine cases, all in males, eight Chinese and one white, all associated with cirrhosis of the liver. The greater frequency of primary carcinoma of the liver in males may be due to the greater frequency

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of cirrhosis of the liver in this sex. It is of interest also that the majority of reported cases of primary carcinoma of the liver have developed as hepatomas, i.e., have arisen from the hepatic cells, and that only a small fraction of cases is reported as cholangeomas.

The case reported here is unusual in that it occurred as a cholangeoma, also in that the patient was a female who had suffered from cirrhosis of the liver for a number of years, and in that the superficial veins of the right side of the abdomen only were enlarged.

Case Report

L. L., a white female, aged 40 years, married, born in Russia, was admitted to the Gastro-Intestinal Service at the Beth-El Hospital, July 16, 1930.

Chief Complaint. Pain in the right upper quadrant on and off for the past two and one-half years; general weakness; loss of weight and vomiting.

Present Illness. For two and one-half years, the patient had been complaining of pain in the right upper quadrant of the abdomen which radiated to the right side and back and at times downward to the right lower abdomen. This pain had become more severe during the last nine months. She also complained of epigastric distress with almost continuous belching. The patient had been admitted to the Mount Sinai Hospital, New York, on March 20, 1930 and was discharged May 1, 1930. There an exploratory laparotomy was done, and a biopsy of the liver was taken. The pathologic report of the biopsy stated that a few cell groups slightly suspicious of tumor cells were found. The diagnosis on discharge was "probably metastatic carcinoma in the liver with unilateral obstruction." After being discharged, her abdomen filled rapidly, and on May 9, 1930 she was readmitted to the Mount Sinai Hospital where two abdominal paracenteses were done to remove the fluid. The patient was discharged on May 30, 1930, this time with the diagnosis "cirrhosis of the liver with ascites"; condition unimproved. Her complaints became more severe and the abdomen filled rapidly. She lost eighteen pounds in weight in eight months' time. For two weeks prior to admission, she had been vomiting two and three times a day with no relation to food. She was admitted to the Beth-El Hospital on July 16, 1930.

Family history and previous personal history were irrelevant, with the exception of an attack of typhus fever at 18 years of age. The patient had been married six years, and had had two still births, one miscarriage and one child, living and well, two and one-half years of age. She dated the pain in the upper right quadrant from the birth of this last child. Since the birth of her child, two and one-half years before, she had not menstruated.

Physical Examination. An adult female, anemic, emaciated, cachectic; abdomen markedly enlarged, out of proportion to the rest of the torso. Eyes reacted to light and accommodation; conjunctivae showed icteric tint. Mouth and throat were negative. Neck showed no adenopathy and no pulsation of vessels. Lungs: dullness to flatness on the right side from the third intercostal space to the base, with the absence of breath sounds in this area; some flatness over the base on the left side and râles in both bases posteriorly. The heart was normal in size, rapid in action, and the sounds were regular and of fair quality. The abdomen, as noted before, was markedly enlarged with dilated superficial veins, showing evidence of collateral circulation, on the right side only. The spleen was not palpable. The liver was markedly enlarged, with an irregular edge; the left lobe was definitely enlarged and irregular. The scar from the previous laparotomy was present and the wounds from the previous paracenteses were noted. All the signs of abdominal fluid were present. The extremities were negative. Vaginal examination showed a tight introitus; the cervix was low, appar-

ently closed and tender to movement; tenderness could be elicited in both fornices; the adnexae were tender to palpation; the uterus could not be felt because of the fluid in the abdominal cavity.

The patient's temperature during her stay at the hospital ranged from 99° to 101° F. The pulse rate ranged from 80 to 126 per minute; the respiration ranged from 20 to 28 per minute. Urine examinations were practically negative. The blood count showed a marked secondary anemia with 45 per cent hemoglobin, 2,800,000 red blood cells and 8,800 white blood cells. There were 76 per cent neutrophiles and 24 per cent monocytes. Blood chemical tests showed 105 mg. of sugar per 100 c.c. blood; 12.5 mg. of urea nitrogen; 1.3 mg. of creatinine; and 210 mg. of cholesterin.

The blood pressure on admission was 124 systolic and 86 diastolic. At subsequent times it fell to 100 systolic and 70 diastolic. The last blood pressure was 96 systolic and 54 diastolic. The Kahn and Wassermann tests were negative on two examinations. A colloidal gold test on the spinal fluid was negative. A Widal hemaclasie test showed impairment of the liver function.

Paracentesis of the abdomen was performed. The ascitic fluid showed a specific gravity of 1.019, three plus albumin and many endothelial cells.

Course in the Hospital. The patient became progressively worse, the liver still more enlarged. Salyrgen was administered with no improvement. In all, five paracenteses were done but the fluid reaccumulated very rapidly. Vomiting, as a rule, was relieved by the removal of the ascitic fluid. Because of the marked loss of weight within a short time and the rapidly enlarging liver, and because of the report of the biopsy done at the Mount Sinai Hospital, a tentative diagnosis of carcinoma in the liver was made. The patient died September 11, 1930.

Autopsy

Body is that of a white female, aged 40 years, weight 95 pounds, five feet two inches in height. The body is still warm and rigor mortis has not set in. Marked loss of weight is evidenced by the dry skin, sunken eyeballs and cheeks, and shriveled extremities. A pitting edema of both ankles is present. A right rectus scar extending from the chondral margin to a distance of 2 cm. from the pubis is seen.

Head and Neck: Not examined.

Abdomen: The peritoneal cavity contains about 2,000 cubic centimeters of a clear straw-colored fluid.

The *stomach* and *intestines* show no ulcerations or areas of new growths. A mass occupying the site of the liver extends to the twelfth rib on both sides. It is irregular, nodular, firm and covered by a thick capsule. The latter is firmly adherent to the anterior abdominal wall and is torn away with difficulty. On section, the cut surface is firm, yellowish white and thrown into irregular islets by intervening strands of yellowish green tissue. Some sections are softer, pinkish and somewhat necrotic.

The *spleen* weighs 220 gm. and the capsule is studded with miliary, whitish, pin-head size areas. On cut section, marked trabeculation and fibrosis are apparent and the splenic pulp is comparatively firm.

The *right kidney* weighs 125 gm., the *left kidney*, 110 gm. The capsule is grey, smooth, and strips with ease, exposing a smooth beefy surface. On section the cortex measures 0.6 cm. and the medulla, 1.7 cm. The striations are somewhat hazy but the pelvis is grey, smooth, glistening and shows no areas of hemorrhage.

Microscopic Examination

1. *Liver:* Multiple sections through each portion of the liver removed present the same appearance. No liver lobular structure is apparent. Here and there a small remnant of liver cord or lobule is present. The cells are generally atrophic. The

sections are all composed of fibrinous connective tissue in which are scattered numerous cell masses of varying size and shape. In places these masses appear as solid sheets of cells, in others as isolated cells generally in narrow linear arrangement, while in still other places irregular alveoli are present. These latter are, however, generally irregular in size and shape, are usually incomplete, in places appear as solid alveoli, and nowhere possess any semblance of a basement membrane, or any thickening of the adjacent fibrous tissue that resembles a limiting membrane. The individual cells composing all these areas are rather difficult to discern because their cell outlines are indistinct, the cells apparently merging particularly in the solid masses. Where best seen (in the alveolar arrangements), they are rather large, irregular, cuboidal cells, possessing a small amount of clear, pale basophilic cytoplasm without granules, and a large round vesicular nucleus in which a single nucleolus is generally quite distinct. These cells resemble bile duct cells. Numerous hyperchromatic nuclei and a few atypical mitoses are present. There are many formless necrotic masses of cells usually in the central portions of the larger cell masses.

The connective tissue is of two types (Van Gieson's stain). The capsule is composed of thick, dense, relatively acellular lymphocyte-infiltrated tissue from which radiate similar strands which separate the cell masses described. Nearer these masses, and particularly in one section showing atrophic adjacent liver tissue, is a more cellular fibrous tissue taking the stain more faintly. Here are numerous capillaries, generally congested, numerous fibroblasts, and but a sparse lymphocytic infiltration. Penetrating in the atrophic (but not neoplasm-involved) lobules, is fibrous tissue of the first type.

2. *Spleen:* Shows a marked widening and congestion of its sinuses, in which, and in whose swollen lining cells, numerous hemosiderin masses are present. The pulp and corpuscles are very narrow, irregular and sparsely cellular; no germinal centers are apparent. The capsule is markedly thickened, of acellular fibrous tissue, in places nodular; the trabeculae and vessels are similarly markedly fibrotic.

3. *Kidneys:* Show no histologic changes other than a moderate intimal hyperplasia of the larger arteries.

Comment

The two types of fibrous tissue present and the subcapsular inflammatory involvement of the liver and its few visible portal spaces, as well as a similar involvement of the few lobules apparent, and the absence of peri-neoplastic inflammatory signs, are suggestive that this neoplasm developed in a liver the site of a previous periportal cirrhosis. The marked splenic congestion and fibrosis are further suggestive signs pointing in this direction. Particularly does the nodular fibrosis in the spleen suggest a very old process, older probably than the average duration of an hepatic neoplasm.

Carcinoma in the small intestines is rare and, according to most authorities, carcinoma in the jejunum is extremely rare. Harris and Rosenblum [7] quote 41,883 necropsies in the Vienna General Hospital, which included 343 cases of intestinal carcinomas; not one case of carcinoma of the jejunum was noted. Baron [8] stated that 8 per cent of total carcinomas occur in the gastrointestinal tract; 4 per cent of this number occur in the small intestines, and the most common site is in the duodenum next to the ileum and rarely in the jejunum. On the other hand, the reports from The Mayo Clinic, as reported by Rankin and Donald,[9] show the incidence of carcinoma of the small intestines as 0.062 per cent of all the carcinomas of the gastrointestinal

tract. They also state that they found the jejunum to be the most common site and the duodenum and the ileum to be involved in equal proportion.

After a thorough perusal of the literature, we believe that there is no characteristic symptomatology of carcinoma of the jejunum. Both the subjective and objective symptoms are really dependent upon the stage of the disease in which the patient is first seen and upon the amount of obstruction present. An interesting fact brought out by Roblee,[10] is that intestinal carcinomas may metastasize to the ovaries. As a rule, the disease is insidious in its onset and causes very little gastrointestinal disturbance until sufficient amount of obstruction is present to produce vomiting. Secondary anemia is usually present. Visible peristalsis may or may not be observed. The tumor mass is not often palpated. The stool may or may not contain occult blood, depending upon the presence or absence of ulceration in the tumor mass. Harris and Rosenblum report that the free hydrochloric acid in the gastric contents is low or absent. Our case, as will be noted later, had a normal amount of free hydrochloric acid.

Case Report

M. M., a white female, aged 40 years, married, born in Russia, was admitted to the Beth-El Hospital on March 24, 1933.

Chief Complaint. Persistent vomiting for the past three weeks, with pain in the upper abdomen.

History. About three years before, the gall-bladder was removed and since that time the patient complained at infrequent intervals of pains in the upper abdomen which became more frequent and more severe during the past three months. The pain was localized in the epigastric region and radiated upward to the substernal region. In the earlier stages of her illness she vomited occasionally, but for three weeks prior to admission to the Hospital, she had vomited persistently throughout the day and frequently during the night. Her appetite had failed; and she complained of belching, pyrosis, and a bad taste. Her bowels as a rule were constipated. She had lost weight. Her sleep was not much disturbed.

The patient had been married for 19 years, and had five children, all living and well. Menstruation was regular. The remainder of the personal history was irrelevant.

Physical Examination. The tongue was coated; the throat, negative. Heart and lungs were normal. The abdomen was tympanitic and showed no marked tenderness or rigidity; no masses were felt. A scar was present from the previous operation.

The urine was negative with the exception of some sugar, due to intravenous glucose injections. The blood chemical tests gave normal results. Wassermann test was negative. Blood count: hemoglobin 77 per cent; white blood cells 8,600; red blood cells 4,100,000; polymorphonuclears 78 per cent; and mononuclears 22 per cent. The gastric analysis, after an Ewald test meal, showed free hydrochloric acid 32 and total acidity 46. Roentgen-ray examination showed retention in the jejunum for 24 hours after ingestion of the barium meal (figure 1).

Because of the history of cholecystectomy, followed by upper abdominal pain, with persistent vomiting, without the presence of any tumor or mass in the abdomen which could be palpated, and with the characteristic picture as shown on the roentgen-ray, a diagnosis of post-operative adhesions was made. These bands of adhesions evidently caused a constriction of some of the upper loops of the small intestines. The possibility of an internal hernia was considered.

The patient was operated upon on April 5 by Dr. Kogut, who found the coils of the small intestine all matted together and partly kinked. With difficulty he separated these coils. High in the jejunum, about six inches from the duodeno-jejunal junction, a mass was felt about 3.5 cm. in diameter with nodules on the peritoneal surface, and below and adjacent a second mass was felt about 1 cm. in diameter, causing a slight constriction in the gut. Distal to the first mass, the jejunum was dilated for a

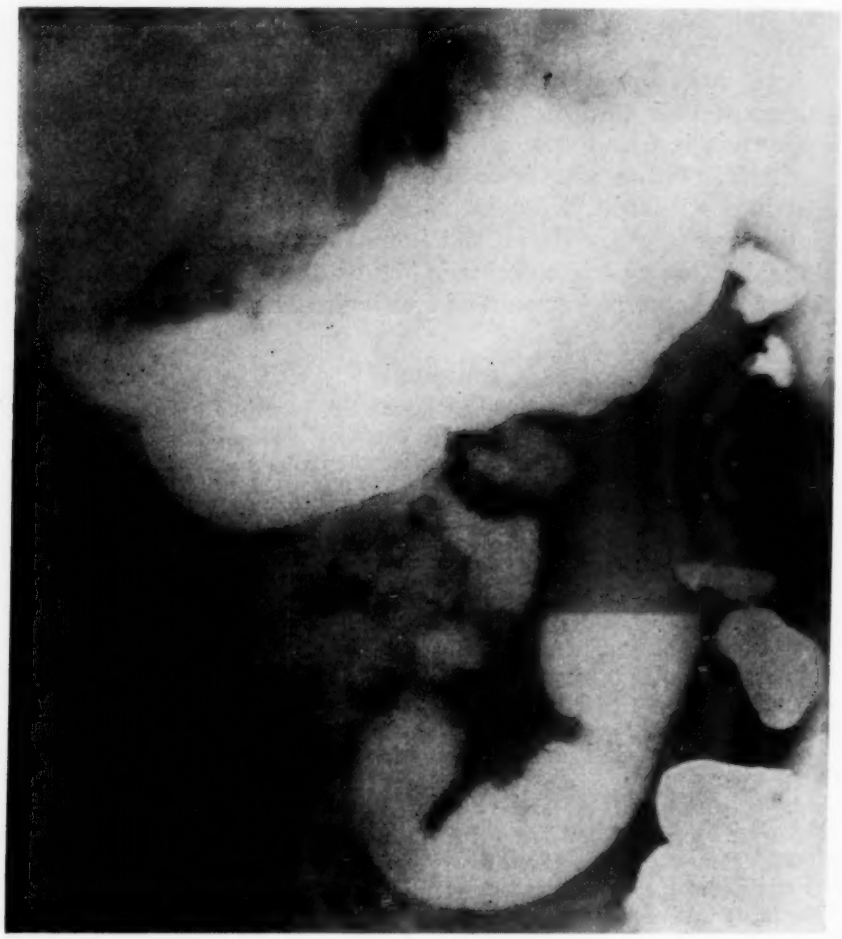

FIG. 1. Roentgen-ray of carcinoma of the jejunum.

distance of 7 cm. at which point there was a stellate puckering constricting the gut and constituting the point of obstruction (figure 2). This area was covered by a fibrinous exudate and the gut below was collapsed. Adjacent lymph nodes were enlarged. The liver was palpated and no gross metastatic nodules were noted. Twelve inches of the jejunum were removed, including the entire mass. An end-to-end anastomosis of the intestines was done. Amniotic fluid was poured into the abdomen to prevent the formation of adhesions and the wound was sutured in layers.

For 15 days the patient did well. The wound was healing by primary union and was clean. The patient improved rapidly, took food by mouth and apparently gained

in strength. On the sixteenth day some foul-smelling material was discharged from the wound due to a superficial infection. The wound was dressed daily and irrigated with peroxide. On April 30, the twenty-fifth day after operation, the wound dressings were found to be saturated with fluid. Within a few days the drainage became very profuse. Food and high intestinal contents were noted in the drained material. Toward the end, the patient herself noticed that the fluid taken by mouth would immediately drain through this opening. The patient died May 7, 1933.

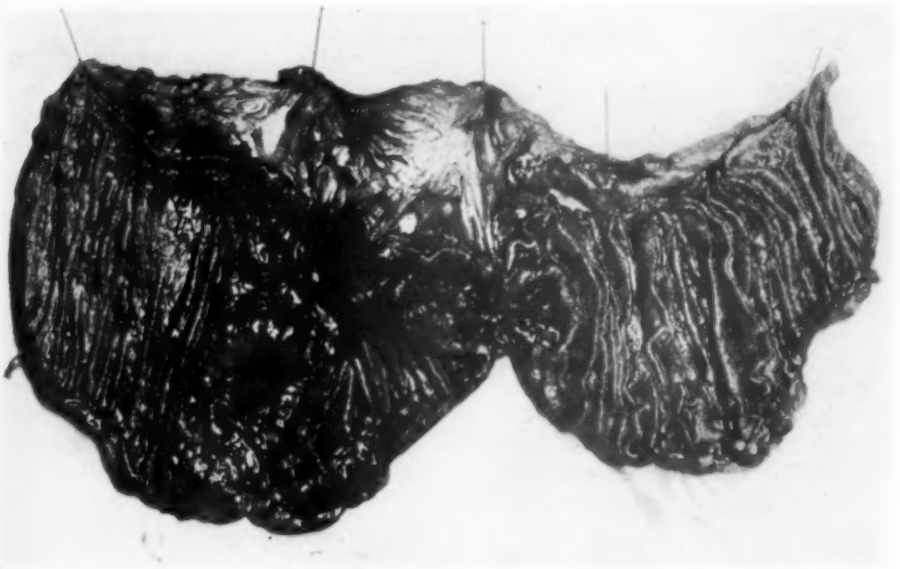

FIG. 2. Carcinoma of the jejunum.

PATHOLOGICAL REPORT

The specimen consists of a portion of jejunum 18 cm. long, with a circumference of 5 to 7 cm. and a thickness of 0.4 cm. A thick mesentery 3 cm. wide is attached. On the serosal surface, 7 cm. from the distal end, there is a stellate, puckered area which constricts the lumen almost to pencil size, measuring 2.5 cm. in diameter. It is covered by a fibrinous exudate on the peritoneal surface. At a distance of 4 cm. from the proximal end, there is a large, pale, raised area with a circumference of 3.5 cm. with small nodules at the periphery, and adjoining this area, at the same level, there is a smaller pale area somewhat constricted, but not raised. The rest of the serosa appears grossly normal (figure 2). The mesentery contains a moderately firm nodule, discrete but not encapsulated, which on section is composed of a smooth succulent homogeneous yellowish tissue. The mucosal surface opposite the constricted area mentioned above shows a stellate arrangement due to distortion of the mucosal folds. The very central portion seems to be devoid of mucosa. In the peripheral portion the wall is thickened. The remaining two areas, corresponding to the pale serosal surface area involvements, present a flattening of the rugae and a markedly thickened mucosa at the periphery. The lumen proximal to the constriction is increased in diameter, while that distal is comparatively normal. On section the layers of the wall are very distinctly made out, showing a widened mucosa, especially at the periphery of the several ulcerated areas.

Microscopic Examination

Section of the small intestinal ulcers shows the mucosa to be thickened, and the lining cells of the surface and glands are markedly increased in size. The mucosa is suddenly interrupted by a crateriform ulcer whose superficial surface is lined by fibrin and cellular débris. The underlying tissue is made up of a markedly cellular tissue with no obvious arrangement or supporting stroma which penetrates or replaces all the intestinal coats up to and including the serosa. The cells spread laterally for a distance of about 1 cm. infiltrating the stroma of the above described mucosa, appearing in linear fashion or in the lymphatics of the submucosa, or as strings of isolated cells between the markedly thickened muscle coats.

The cells present no particular arrangement, growing in solid masses in the vicinity of the ulcer and distributing themselves haphazardly along tissue spaces or lymphatics at distances from the main mass. The cells vary from round or polyhedral to slightly elongated ovals and approximate each other with intervening stroma in the large masses but are isolated by preëxisting connective tissue as they spread further from the ulcerated area. The cytoplasm is scant, faintly eosinophilic and occasionally distended with clear material. The nuclei are large, vesicular, with one or two prominent acidophilic nucleoli; normal and atypical mitoses occur but not frequently. The small serosal mass is an edematous lymph nodule showing moderate fibrosis in the cortical area where small numbers of widely disseminated tumor cells are also seen. Throughout the sections, the tumor cells are accompanied by a slight round and plasma cell exudate, and a very moderate fibroblastic reaction. Degeneration of tumor cells is seen only at the very surface of the ulcerative area.

Diagnosis. Primary carcinoma simplex in the jejunum, infiltrative and perforating. The encephaloid growth, and the wide dissemination with lack of exudative or proliferative reaction, indicate a tumor of a high degree of malignancy.

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EDITORIALS

PRIMUM NON NOCERE

THE MEDICAL literature of the last few years contains many articles which tend to induce caution in the use of drugs.

A careful restudy of digitalization in pneumonia has indicated that it is probably detrimental to the patient's chances of recovery rather than helpful.[1] Cinchophen has been found to produce very troublesome urticaria and not infrequently a fatal degree of hepatic injury. A very considerable number of deaths from this cause are now recorded. Potassium thiocyanate, widely used as a helpful palliative in hypertension, has been shown to be responsible for instances of exfoliative dermatitis, and occasionally to cause toxic deliria, coma, and even death.[2] Amidopyrine and barbiturates in combination are now under definite suspicion of having brought about much of the increased incidence of malignant neutropenia noted in recent years.[3]

There is at present active interest in the clinical use of alpha-dinitrophenol as a remedy in obesity and no doubt but what it is being widely used throughout the country. This drug has been shown to cause a rapid and considerable increase in the rate of oxidative metabolism. Accompanying the increase in oxygen consumption and heat production there is a decrease in liver and muscle glycogen, an increase in muscle and blood lactates and a rise in blood sugar, all of which suggest that carbohydrate oxidation is accelerated. It is estimated, however, that less than half of the oxygen consumption can be accounted for in this manner. Since patients were observed to maintain a slightly positive nitrogen balance while taking the drug and losing weight, it may be assumed that excess oxidation of protein does not occur to any considerable extent. This would lead to the conclusion that close to half of the oxygen is consumed in the oxidation of fat. Since the urine contained no increase in organic acids it may be inferred that the fat was broken down completely to carbon dioxide and water. Insofar, then, as the details of the increased oxidations due to alpha-dinitrophenol are known they resemble physiologic oxidations.

If the rate of oxidation is such as to produce heat beyond the power of the heat regulating mechanism to dissipate, the body temperature will rise. Fatal hyperpyrexia occurs in man and experimental animals following an excessive dosage. In therapeutic doses, however, the drug does not cause fever. Concerning the toxicity of the drug it has been reported that its administration to dogs for from two to three months in doses just short of fatal has not resulted in significant injury to important organs as shown

[1] NILES, W. I., and WYCKOFF, J.: Studies concerning digitalis therapy in lobar pneumonia, Am. Jr. Med. Sci., 1930, clxxx, 348–356.

[2] GOLDRING, W., and CHASIS, H.: Thiocyanate therapy in hypertension. I. Observations on its toxic effects, Arch. Int. Med., 1932, xlix, 321–330.

[3] MADISON, F. W., and SQUIER, T. L.: The etiology of primary granulocytopenia (agranulocytic angina), Jr. Am. Med. Assoc., 1934, cii, 755.

by studies of the urine, icteric index, van den Bergh test, and organs at autopsy and tissues microscopically. Moreover clinical trial of the drug was felt to show that in therapeutic doses it caused none of the undesirable stimulating effects on the circulation and the autonomic nervous system which result from thyroid extract.

On the basis of these data, Cutting, Mehrtens and Tainter [4] employed alpha-dinitrophenol in the treatment of obesity and published their first clinical report in July 1933. In view of the satisfactory results obtained in eight cases, they felt that extended clinical trials in this condition were justified but expressly warned against the possible toxic effects which might appear after prolonged use, against the possibility that in some disease conditions the drug might be poorly tolerated, against the possibility of idiosyncrasy to the drug, and against the danger of hyperpyrexia from excessive dosage.

Such warnings were needed, for the actions of this potent drug were only partly known, and what was known had a striking appeal both to the clinician and to the patient. It seemed possible that here was a substance to simplify the whole trying problem of treating the obese. If, in the past, people had been unequal in their ability to accelerate their metabolic rates in response to excess nutrition, and so to remain lean in spite of overeating, here in a drug was a means by which the sluggish could be stimulated and luxus consumption be provided for them in a capsule.

Since the original paper of Cutting, Mehrtens and Tainter further reports have appeared dealing with the clinical use of the drug. Tainter, Stockton and Cutting [5] published a progress report in November 1933 on the results of treatment in 113 consecutive cases of obesity. The average daily dose of dinitrophenol given in capsules was 290 mg.; the average duration of treatment was 40 days; and the average loss of weight was 8.8 pounds. The lack of definite data as to the diet diminishes the value of these figures. Anderson, Reed and Emerson,[6] after using the drug in 14 cases, kept on a diet limited to foods low in sugars and fats, noted an average weight loss for the first month of therapy of 2.3 kg. and for the second month of 2.1 kg.

Meanwhile it has become evident that, even with doses thought to be safe, patients might exhibit definite toxic symptoms. Nine of the 113 cases treated by Tainter, Stockton and Cutting were forced to discontinue the drug because of unpleasant reactions. Others persisted in its use in spite of definite toxic effects. Four complained of shortness of breath, six developed disturbances of the sense of taste, three had gastrointestinal upsets and eight broke out with a troublesome urticarial eruption and edema lasting

[4] CUTTING, W. C., MEHRTENS, H. G., and TAINTER, M. L.: Actions and uses of dinitrophenol, promising metabolic applications, Jr. Am. Med. Assoc., 1933, ci, 193–195.

[5] TAINTER, M. L., STOCKTON, A. B., and CUTTING, W. C.: Use of dinitrophenol in obesity and related conditions, Jr. Am. Med. Assoc., 1933, ci, 1472–1475.

[6] ANDERSON, H. H., REED, A. C., and EMERSON, G. A.: Toxicity of alpha-dinitrophenol, Jr. Am. Med. Assoc., 1933, ci, 1053–1055.

from two to five days after withdrawal of the drug. The authors do not appear to have been impressed with the gravity of these skin manifestations. Anderson, Reed and Emerson report a more severe skin reaction of the same type.

Masserman and Goldsmith [7] employed dinitrophenol under carefully controlled conditions in 18 mental cases characterized clinically by sluggishness, passivity and apathy. They observed in five cases a type of toxic reaction consisting of falling blood pressure, tachycardia, acidosis, and progressive stupor. In one case death ensued.

By analogy with the experience with other drugs it may safely be assumed that these reported instances of toxic action of dinitrophenol probably represent only a fraction of those that have occurred. How long it may take the general profession to realize the toxicity of a drug, or be moved to report examples of such toxic action, is well illustrated in the case of cinchophen. This drug was introduced into medicine in 1909. In 1926 Hanzlik [8] published an exhaustive review of the actions and uses of salicylates and cinchophen in medicine. He stated therein under the heading of toxicity: "The literature contains no reports of fatalities from cinchophen and its derivatives."

The practicing physician will do well in the case of alpha-dinitrophenol to consider carefully whether experimentation with this drug had not best be confined for the present to the carefully controlled conditions of research clinics.

AIR TRAFFIC AND DISEASE

In recent years while our communications with the tropical regions to the south of us were still confined almost entirely to travel by ship the danger of importation of tropical diseases, while considerable, as early experience with yellow fever indicated, has proved controllable through the vigilance of the Public Health Service at the ports of entry. The time factor involved in travel by sea is of material aid in that control in that during the voyage disease usually passes from the stage of incubation to that of manifest symptoms and is more readily detectable upon arrival at quarantine. Moreover the simple fact that the vehicle of transport, the ship, does not in a true sense enter the country facilitates its isolation from the community when this is necessary, and makes it possible to prevent to a large extent the passage to shore of disease-carrying humans, insects and rodents.

It is apparent that the rapid development of air routes connecting this country with the West Indies, and Central and South American countries offers new problems in public health. The speed of the planes nullifies the safety factor in slower travel, and passengers may be widely scattered in various parts of the country before they become manifestly ill. Moreover

[7] Masserman, J. H., and Goldsmith, H.: Dinitrophenol; its therapeutic and toxic actions in certain types of psychobiologic underactivity, Jr. Am. Med. Assoc., 1934, cii, 523–525.
[8] Hanzlik, P. J.: Actions and uses of the salicylates and cinchophen in medicine, Medicine, 1926, v, 197–373.

since the landing fields cannot be isolated, infected insects or rodents carried in the plane may readily escape into the surrounding community.

The Public Health Service has been actively investigating certain of these possibilities.[1] Inspections of airplanes arriving in Miami from Cuba, Panama and other points in Central and in South America have led to the capture and identification of a rather limited number of mosquitoes of many species including the *Aedes aegypti*. Moreover mosquitoes of this latter species were bred, fed on human blood, stained by spraying with 2 per cent eosin and then liberated in the various compartments of cabin planes prior to their departure for Miami or Brownsville. Mosquitoes thus placed on board in San Juan, P. R., San Salvador, and Cristobal, C. Z., were identified in the planes on arrival at the above ports of entry in spite of numerous stops en route. The number captured and identified was usually a small percentage of the total.

The inspection of planes also revealed the presence of house flies, honey bees, and cock roaches. Rat droppings were observed but the rats themselves were not found.

The investigators concluded that it had been demonstrated that the known yellow fever and dengue vector of the western hemisphere may be carried with facility from and to countries in which there were formerly endemic or epidemic centers. Comprehensive but not too rigid or unreasonable sanitary regulations they feel will be required. These should include (1) the proper surveillance of passengers and crews of aircraft coming from infected localities, (2) anti-mosquito sanitation at airports and their environs, and (3) proper precautions to prevent mosquito and other insect harborage in aircraft and the destruction of mosquitoes on aircraft upon or after leaving airports. Such measures need in no way retard air traffic progress.

The importation of infected man probably offers a more important problem. In many of such instances the inspection at the port of entry will be fruitless and the responsibility of recognition of the imported disease will fall upon the second line of defense, the family physician.

[1] Griffitts, T. H. D.: Air traffic in relation to public health, Am. Jr. Trop. Med., 1933, xiii, 283–290.

REVIEWS

The Modern Treatment of Syphilis. By JOSEPH EARLE MOORE, M.D. 535 pages; 17 × 26 cm. Charles C. Thomas, Springfield. 1933. Price, $5.00.

When an important problem such as the treatment of syphilis is in a constant state of flux and possesses a very large and widely scattered literature, the appearance of an authoritative book on the subject is sure to meet with a good reception from the medical public. This is even more certain if the author does not present a mere summary of all possible methods of treatment but discusses in satisfying detail those methods which he considers best and the results that have been obtained with them.

This book represents the outcome of experience in the treatment of over 18,000 cases in the Syphilis Division of the Medical Clinic of the Johns Hopkins Hospital. This material has been very carefully studied by the author, who is Chief Physician, and his associates, and the results have been the subject of numerous earlier publications. Contributions from the Coöperative Clinical Group, representing the Syphilis Clinics at the University of Pennsylvania, The Mayo Clinic, the University of Michigan, Western Reserve University, the Johns Hopkins University, and the United States Public Health Service, are also cited extensively in evaluating the results of treatment. The general literature is adequately considered.

The earlier chapters are given up to general considerations affecting the problem of therapy; the biology of syphilitic infections, prognosis in the treated and untreated, the appraisal of the problem in the individual case. The essential pharmacology of the chemotherapeutic agents is outlined and the technic of their administration given in detail. The latter two-thirds of the book are then devoted to a discussion of treatment and its results in early and in late syphilis, in latent syphilis, and in syphilis involving the cardiovascular system, the eye, the viscera, the nervous system, etc. The treatment of congenital syphilis, of syphilis in pregnancy, and of syphilis complicated by other diseases are dealt with in separate chapters.

The author has definite ideas on all these questions; his point of view is conservative; he has evidence to offer for the statements he makes. His book is clearly written. The reviewer feels that it will become a standard reference on the treatment of syphilis and that it may be highly recommended to all physicians.

M. C. P.

The Doctor Discusses Your Questions. By MARK GERSTLE, JR., M.D., Assistant Clinical Professor in Neurology, University of California Medical School, San Francisco, Calif.; with a foreword by LANGLEY PORTER, M.D., Dean of the University of California Medical School. 91 pages; 11 × 15.5 cm. J. W. Stacey, Inc., San Francisco. 1933. Price, $1.00.

This little book is intended for the lay reader and presents in a clear simple manner many important facts relating to medicine and health. Such topics as infection and immunity, diet and nutrition, drugs and treatment, cancer, sex and venereal diseases are discussed in a common sense, practical way. A short chapter devoted to adjustments and maladjustments should be especially helpful. This book may be recommended without hesitancy to patients.

A. C. G.

Birth Control in Practice: Analysis of 10,000 Case Histories of the Birth Control Clinical Research Bureau. By MARIE E. KOPP, Ph.D., under an advisory committee composed of seven physicians, and a foreword by ADOLF MEYER, M.D. 290 pages. Robert M. McBride and Co., New York. 1934. Price, $3.75.

Adolf Meyer well says in his foreword that this volume " furnishes an example of what can be done in the future to keep account of procedures through which man

is assuming a very real and far-reaching responsibility for the cultivation of the welfare of mothers and children as well as those entitled to be fathers. . . . Facts in all sorts of directions are called for, if we are to emerge from the drastic domination of negation, of prohibition, and of corresponding dishonesty and bootlegging and its . . . uncontrollable accompaniments. Without facts we can form no judgment of the dependability of what is held up to us as an example of valid practice and constructive service." This volume certainly has succeeded in presenting scientific facts impartially.

The book is divided into four parts. The first takes up the method of collecting material; the second, sociologic and economic factors; the third, analysis of physical factors; and, fourth, indications for postponement or prevention of pregnancy. The material in this book is based on the 10 years of social and medical data compiled from the records of a birth control clinic in New York City, the contraceptive advice having been furnished by this clinic only in cases definitely within the limits of the law of New York State and, therefore, the accepted indications were essentially medical.

The religious affiliations of the women studied showed that 42 per cent were Jewish, 30 per cent Protestant, and 26 per cent Catholic; four-fifths of the husbands belonged to the industrial and clerical groups, while only one-fifth fell in the professional class. It is worthy of note that only 1 per cent of the patients were under 20 years of age, more than half had had four or five pregnancies during an average of eight and one-half years of marriage, and at least half of the cases had had their first pregnancy before they were 22 years old.

Only one in fifteen of the couples had not used some form of contraception before the women came to the clinic, and most of these methods were found to be the types generally showing medical contra-indication. Every woman before receiving advice was given a careful gynecological examination, and there is no doubt that one of the great values of this clinic work was the early detection of disease, both constitutional and local. Of those being given a prescription for contraception, the methods applied were found to be 93.3 per cent successful.

J. L. McC.

Recent Advances in Endocrinology. By A. T. Cameron, M.A., D.Sc. (Edin.), F.I.C., F.R.S.C. vii + 365 pages; 14 × 21 cm. P. Blakiston's Son and Co., Inc., Philadelphia. 1934. Price, $3.50.

This small volume by a well known biochemist summarizes in a very satisfactory way the status of investigative work in endocrinology up to the end of 1932. It will prove a real boon to the internist who feels acutely the need of keeping abreast with the advances in this rapidly developing field but finds it impossible to cover the overwhelming literature of the subject. Essentially this book is an orderly classification of the recent literature on the nature and function of the endocrine compounds of the thyroid, parathyroid, pancreas, adrenals, pituitary and organs of reproduction. Under each heading come topical discussions of the questions most actively studied in recent years. Where there are sufficient data available to warrant it, the author undertakes an analysis of the present status of the particular problem. His succinct and conservative comments add greatly to the value of the book.

There is a chapter on "Some Actual and Presumptive Endocrine Principles," and a final chapter on "Endocrine Interrelationships."

The numerous and apparently well chosen references are arranged at the end of each chapter.

M. C. P.

Recent Advances in Vaccine and Serum Therapy. By ALEXANDER FLEMING, F.R.C.S. (Eng.), and G. F. PETRIE, M.D. (Aberd.). x + 463 pages; 14.5 × 21 cm. P. Blakiston's Son and Co., Inc., Philadelphia. 1934. Price, $4.00.

The authors have produced a very interesting book on the present status of vaccine and serum therapy in the astonishingly long list of diseases in which these therapeutic agents are currently employed. There is probably no field of therapy in which the practicing physician feels less certain of his ground. His use of sera, except in times of certain epidemics, is comparatively limited and, since the occasions for their use are apt to be in the nature of emergencies, he should welcome this compact account of the more recent information available as to the value and disadvantages of their administration in specific conditions. Unfortunately even with these data at hand he will not find himself delivered from uncertainty and conflicting reports; but at least he may make his decisions on a sounder basis of knowledge. There is a very similar value to the section on vaccines.

In reading various sections of this book, one is impressed with the thoroughness of the treatment and by the frequent mention of work published as late as 1933. It is apparent that the serum treatment of pneumonia has not been employed as extensively in Great Britain as in the United States; this chapter is not as full as might be desired. It seems also unfortunate that apparently because of lack of recent advances in our knowledge of smallpox vaccination this subject is omitted entirely.

The book is a very valuable reference volume for the internist and it deserves a place in the working library of every hospital laboratory.

M. C. P.

Hospital Medical Statistics. By CAROLINE R. MARTIN, M.D., Director, Central Medical Statistical Bureau, New York Department of Hospitals. 89 pages. J. B. Lippincott, Philadelphia. 1933. Price, $1.00.

This small handbook gives a brief description of the system of hospital statistics used in the Department of Hospitals in the City of New York and it describes an up-to-the-minute method of securing this very important material. Most hospitals compile some form of case histories but "surprising little thought seems to have been given to the question of what to do with these records after they have served their immediate purpose in the treatment of patients. Obviously these millions of individual case histories must contain the answer to many pressing problems both medical and administrative."

Every hospital should have a copy of this booklet, and the private physician will also find some interesting facts within its pages for it points out the important fact that "statistics to be truly valuable must be quantitative as well as qualitative; only then do they furnish a reliable yardstick of trends and probabilities."

J. L. McC.

Observations of a General Practitioner. By WILLIAM N. MACARTNEY, M.D., Ft. Covington, N. Y. 478 pages. Gorham Press, Boston. 1932. Price, $3.00.

The last few years much discussion has been carried on about the disappearance of the general practitioner, and there is no doubt that most medical literature has been contributed by specialists. It is, therefore, stimulating to have the opportunity of reviewing this book which is the product of a general practitioner of long experience.

Dr. Macartney graduated from New York University Medical School in 1888, and in his book he vividly tells of how he changed his mind from being a city physician to settling down as a country practitioner. One has but to mention the fact that

Dr. Macartney is of Scotch-Irish ancestry and still in active practice to recommend this book for its sense of humor and continuity of common sense.

It is seldom that one can find within so few pages such a mass of practical information, for the author in his 90 concise chapters takes the reader from establishing a practice to the realm of "specialism"; from "baldness" to "foot troubles"; from the "contagious diseases" to "arteriosclerosis"; from "diarrhea" to "constipation"; from "strabismus" to "leukorrhea," and from "prescriptions" to "medical superstitions."

One might think that the reader would be bored by the condensation of factual material. But the author's good humor retains the reader's interest from cover to cover, for Dr. Macartney in recording the anecdotes of his wide experience accompanies every incident with a human interest touch.

Although not all internists will agree with everything this veteran general practitioner says, nevertheless this book can be highly recommended for its catalytic effect. It will inspire the young physician to higher ideals and compliment the elite of the profession.

J. L. McC.

COLLEGE NEWS NOTES

Gifts Acknowledged

Acknowledgment is made of the receipt of the following donations by members to the Library of the College by the authors:

Dr. E. B. Krumbhaar (Fellow), Philadelphia, Pa.—1 book, "Clio Medica—Medicine in Canada";

Dr. Harold Swanberg (Fellow), Quincy, Ill.—1 book, "Radiologic Maxims";

Dr. Crawford R. Green (Fellow), Troy, N. Y.—2 reprints;

Dr. Henry J. John (Fellow), Cleveland, Ohio—5 reprints;

Dr. Donald S. King (Fellow), Boston, Mass.—5 reprints;

Dr. Albert E. Russell (Fellow), Knoxville, Tenn.—2 bulletins and 2 reprints;

Dr. J. W. Torbett (Fellow), Marlin, Texas—2 reprints;

Dr. F. Lowell Dunn (Associate), Omaha, Nebr.—10 reprints.

New Life Member

Dr. Philip I. Nash, Brooklyn, N. Y., is added to the list of Life Members of the College as of March 16, 1934.

Dr. Charles Godwin Jennings Honored

On February 28, at the Book-Cadillac Hotel, Detroit, a dinner was given by the Wayne County Medical Society in honor of Dr. Charles Godwin Jennings (Master). Dr. Jennings has been engaged in the active practice of medicine for fifty-five years. His record is a long and honorable one. He has been the recipient of the honorary degrees of Master of Arts from the University of Michigan, and Doctor of Science from the College of the City of Detroit.

Born in the State of New York in 1857, Dr. Jennings received his preliminary education in the schools of Seneca Falls and at Mynderse Academy. He graduated from the Detroit College of Medicine in 1879. From 1881 until 1918, he was connected with the Detroit College of Medicine in successive teaching positions, including lecturer on chemistry, lecturer on chemistry and diseases of children, lecturer in physiology and diseases of children, professor of pediatrics and professor of medicine. He is attending physician and chairman of the Board of Trustees and of the Medical Board of the Charles Godwin Jennings Hospital, consulting physician to the Harper Hospital, Grosse Pointe Cottage Hospital, the Children's Free Hospital, Detroit Tuberculosis Sanitarium and the U. S. Marine Hospital. A recital of all of his activities and appointments is quite beyond the limit of these columns. He has been a life long student, and he has been a most successful teacher, whose clinical lectures were marked by thoroughness in preparation and clarity in presentation.

Dr. Jennings has for many years taken an exceedingly active part in the American College of Physicians. He became a Fellow in 1916, and was honored with a Mastership in 1929. He has served on the Board of Regents for several years, and he is at present First Vice-President and Chairman of the Committee on Public Relations. He was formerly Associate Editor of the Annals of Clinical Medicine, official publication of the College, now known as the Annals of Internal Medicine. He was Chairman of the Detroit Clinical Session of the American College of Physicians and President of the American Congress of Internal Medicine in 1926.

On behalf of the American College of Physicians, Dr. George Morris Piersol,

President, attended the dinner on February 28 and was one of the speakers. Other speakers included Dr. A. W. Blair, President of the Wayne County Medical Society, Hon. James O. Murfin and Mr. Harry M. Nimmo, Editor of the *Detroit Saturday Night.*

Dr. Torald Hermann Sollmann Honored

On February 10 at the Cleveland Club, Dr. Torald Hermann Sollmann (Fellow), Dean of the School of Medicine of Western Reserve University, was honored, on the occasion of his sixtieth birthday, by a luncheon given by the members of the staff. He was presented with a decorated parchment manuscript which was composed by Dr. Howard T. Karsner (Fellow): "To Torald Hermann Sollmann, your colleagues have gathered together to felicitate you upon the occasion of your sixtieth birthday, to congratulate you upon the scientific achievements which have given you eminence the world over. Your academic career, begun and continued in Western Reserve University, has brought luster to your name and distinction to the institution, which through many channels, you have served selflessly, faithfully, enthusiastically, energetically, and with inspiring loyalty. With affection, admiration, and respect, we wish you many more years of fruitful investigation and happiness."

Born in Coburg, Germany, Dr. Sollmann was educated in the Gymnasium there and studied chemistry and pharmacy in Paris. Coming to America, he was graduated from the School of Medicine of Western Reserve in 1896, became at once a member of the teaching staff and has served continuously since, becoming professor of pharmacology in 1904 and Dean in 1928. He is an international authority on pharmacy and materia medica, and has written many books and held offices of the greatest importance in his profession, including membership on the Council on Pharmacy and Chemistry of the American Medical Association and President of the American Society of Pharmacology and Experimental Therapeutics.

Under the editorship of Dr. Frank Smithies (Master), Chicago, and the supervising editorship of Dr. Beaumont S. Cornell (Fellow), Fort Wayne, Ind., the *American Journal of Digestive Diseases and Nutrition* has recently appeared. The editorial council, which contains the names of many Fellows of the College, is divided into several subsections; each subsection containing men particularly capable of guiding the policies of the Journal.

The first issue contains eight to ten important, well chosen and high grade original contributions by men whose names are synonymous with good work in the field of digestive diseases and nutrition. The illustrations are of excellent character and well selected.

Dr. H. B. McCorkle (Fellow), Colorado Springs, Colo., addressed the Missouri-Pacific Congress of Physicians at Memphis recently on "Oxyperitoneum as an Adjunct in the Treatment of Tuberculous Recta! Diseases."

Dr. A. F. R. Andresen (Fellow), Clinical Professor of Medicine (Gastroenterology), Long Island College of Medicine, Brooklyn, N. Y., recently addressed the Suffolk County Medical Society, Patchogue, L. I., on "Peptic Ulcer."

Dr. Andresen delivered a series of lectures on gastrointestinal subjects during October and November 1933, as a part of the program of the postgraduate course before the Rockland County Medical Society at Pomona, New York.

Dr. John B. D'Albora (Fellow) and Dr. Frederick Schroeder (Fellow), also

of the staff of the Long Island College Hospital, were other lecturers on gastro-intestinal subjects given in connection with this postgraduate course.

Dr. Joseph L. Gilbert (Fellow) has been appointed Alienist of the District of Columbia. He also holds the position of Chief Psychiatrist, Gallinger Municipal Hospital, Washington, D. C., and was formerly a Medical Officer at St. Elizabeth's Hospital.

Dr. Gilbert is a former President of the Washington Society for Nervous and Mental Diseases. He is a Fellow of the American Psychiatric Association, and at present is a member of the Executive Committee of the Section on Neurology and Psychiatry of the Medical Society of the District of Columbia.

Dr. E. J. G. Beardsley (Fellow), Philadelphia, Pa., was a guest speaker, February 13, at the meeting of the Lehigh County Medical Association at Allentown, Pa., his subject being "The Golden Rule in Medicine."

During January, Dr. Beardsley delivered a series of public health lectures in the public schools of Mt. Carmel, Sunbury and Shamokin, Pa.

Dr. Roger M. Choisser (Fellow) has retired from the Medical Corps of the U. S. Navy and is now full-time Professor of Pathology at the George Washington University School of Medicine.

Dr. Walter A. Bastedo (Fellow), New York, N. Y., addressed the Bridgeport (Conn.) Medical Society, February 26, on "Persistent or Recurring Inflammatory Diarrheas."

Major Alva B. McKie (Fellow), M. C., U. S. Army, has been recently transferred from the Sternberg General Hospital, Manila, P. I., to Fort Francis E. Warren, Cheyenne, Wyoming.

Dr. Arthur A. Herold (Fellow) has been appointed as councilor of the Southern Medical Association in Louisiana.

Dr. Samuel Weiss (Fellow), of New York, has been elected "membre correspondant de la Societe de Gastroenterologie" of Paris.

OBITUARIES

DR. ROGER SYLVESTER MORRIS

Dr. Roger Sylvester Morris (Fellow), Professor of Internal Medicine and Director of the Medical Clinic of the University of Cincinnati, died suddenly on March 1, 1934. In him the profession loses an eminent teacher and consultant, a brilliant investigator and clinician, a beloved friend.

Dr. Morris was born September 24, 1877, at Ann Arbor, Michigan, the son of George Sylvester Morris, Professor of Philosophy, and Victoria Celle Rogers. He received his A.B. degree in 1900 and his M.D. degree two years later, both from the University of Michigan. Following his graduation he was made Instructor in Medicine at his Alma Mater. He spent the winter of 1903 on the medical service of William Osler, attending his rounds and lectures. It was then that he became a great admirer and friend of Dr. Osler's and here began also his lifelong friendship with the late William Sydney Thayer. He spent the summers of 1904 and 1906 on the medical service of Professor Friederich von Mueller of the University of Munich.

In 1906 he was appointed Assistant Resident Physician at the Johns Hopkins Hospital and Associate in Medicine at the Johns Hopkins University. The following year he married Mary Bledsoe Carter of Baltimore. During his stay at Hopkins, Dr. Morris was in charge of the Department of Clinical Microscopy, a position which had much to do with the publication of his book on "Clinical Laboratory Methods" in 1913. In 1911 he left Baltimore to become Associate Professor of Medicine at the Washington University Medical School, St. Louis. In 1913 he was appointed Chief of the Division of Internal Medicine at the Clifton Springs Sanatorium, New York. In 1915 he was made Professor of Medicine at the University of Cincinnati and Director of the Medical Clinic, Cincinnati General Hospital, positions held until the time of his death. Following his appointment, he received a congratulatory note from the late Sir William Osler,—a missive which he always cherished.

Dr. Morris was a member of the Association of American Physicians, American Society for Clinical Investigation, Central Society for Clinical Research, American Medical Association and a member of its Council on Scientific Assembly for many years, Ohio State Medical Association and the Cincinnati Academy of Medicine. He became a Fellow of the American College of Physicians during 1929. Dr. Morris was also a member of the Alpha Omega Alpha, Sigma Xi, Psi Upsilon, Nu Sigma Nu, University Club and the Cincinnati Country Club.

During the World War he was a Lieutenant Colonel in the Medical Corps and served in France. From 1924 to 1933 he was Chief Medical

Consultant of the Cincinnati Diagnostic Center of the United States Veterans Bureau.

Though handicapped by ill health for many years, he succeeded in building up a Department of Medicine which, judged by the men he has trained and the contributions which he and they have made, should insure him lasting fame. Of his more important contributions to medical science may we allude to "Percussion and Roentgen-Ray Findings after Injection of the Pericardium," "The Physical Findings of Pericarditis with Effusion," "The Clinical Recognition of Pulsus Alternans," "The 'Thyroid Heart' with Low Basal Metabolic Rate" and "The Hematopoietic Response in Pernicious Anemia Following the Intramuscular Injection of Gastric Juice." His last contribution on the effects of injection of concentrated gastric juice led to an invitation to present the Alvarez Lecture before the 1934 meeting of the American Gastro-Enterological Association, an honor precluded by his untimely death.

As a gentleman and a man, Dr. Morris was a distinguished and charming personality. His great dignity commanded respect, his gentleness and modesty brought him loyalty and affection from patients and associates. Both the older and younger men of his staff were quickly and deeply influenced by these characteristics and became devoted and admiring friends of "the chief."

Dr. Morris did much to perpetuate the influence of Osler, Billings and Thayer in American Medicine. He was largely instrumental in establishing the William Sydney Thayer and Susan Read Thayer Lectureship in Clinical Medicine at the Johns Hopkins Hospital in 1927. He was a constant source of encouragement and inspiration to the younger medical men. His deep human sympathy and delightful sense of humor will never be forgotten by those who knew and loved him. As has been said of the late Dr. Thayer, Dr. Morris to us was "the most gracious of men, inspired by a rare generosity; the sweetness of his nature and the simplicity of his character were beyond measure."

It is with a profound sense of personal sorrow that these resolutions of grief and respect are presented at the death of one of the greatest physicians that America has produced.

MARK A. BROWN, M.D., F.A.C.P.,
MONT R. REID, M.D.,
LEON SCHIFF, M.D.

MAJOR PAUL EDGAR McNABB

Major Paul Edgar McNabb (Fellow), Medical Corps, U. S. A., died at Walter Reed General Hospital, Washington, D. C., on February 24, 1934, of a rapidly progressive hypertensive disease and cerebral hemorrhage. He

was born in Sevier County, Tennessee, May 23, 1887, but at the age of five years moved with his parents to Knoxville, Tennessee, his boyhood home. He graduated in medicine at the University of Pennsylvania in 1912 and returned to his home city where he practiced medicine for several years with his father, Dr. Charles P. McNabb, a distinguished physician in Knoxville and widely known consultant throughout the State of Tennessee.

Major McNabb was an honor graduate of the Army Medical School in 1917 and served overseas in France during the World War. He graduated from the advanced course, Army Medical School, in 1921 and was assigned to the laboratory service of the Medical Department where he served with distinction in many difficult assignments, including the Second Corps Area Laboratory, New York; Board of Health Laboratory, Ancon, Canal Zone; Walter Reed General Hospital and the Army Medical School. During this service he achieved the distinction of being regarded as one of the outstanding pathologists in the Army Medical Corps. He was Curator of the Army Medical Museum from February 1931, to January 1933, and was President of the U. S. Army Medical Department Research Board in Manila, P. I., at the time he was stricken with the illness which forced him to return to the United States.

Always interested in research, he published articles on Post-Measles Pneumonia; Quinine Prophylaxis in Army Troops in the Canal Zone; Coronary Sclerosis in Angina Pectoris and the Presence and Significance of Albuminuria in the Personnel of a Citizens Military Training Camp. In collaboration with others he published articles on Hemochromatosis and Congenital Heart Block.

Major McNabb was elected a Fellow of the American College of Physicians in 1930. He was also a Fellow of the American Medical Association and a member of the American Association of Pathologists and Bacteriologists, the International Association of Medical Museums and the National Board of Medical Examiners representing the U. S. Army Medical Corps. He was also an honorary life member of the Knox County Medical Society.

An indefatigable worker for the interests of the Laboratory service, Major McNabb was keenly interested in the welfare and advancement of its personnel, especially the junior members of that service. Possessed with professional ability, charming personality and more than ordinary tact he quickly obtained the friendship and respect of those who were priviliged to be associated with him. His untimely death during the years of greatest productivity is a distinct loss to the Medical Corps.

In 1913 he married Miss Therese Franz of Knoxville, Tennessee, who, with their daughter, Jane Cordon McNabb, aged 17, survive him.

V. H. Cornell, M.D., F.A.C.P.,
Major, Medical Corps, U. S. A.

DR. FRANK CHAMBLISS JOHNSON

Dr. Frank Chambliss Johnson (Fellow, 1931), New Brunswick, N. J., born February 6, 1894, died January 1, 1934, following a fall from chimney rock near New Brunswick, where he had gone to study the geological formation.

After his preliminary schooling at New Brunswick, he entered Rutgers University, graduating in 1916. He pursued his medical training at Columbia University College of Physicians and Surgeons, graduating with the medical degree in 1920. He served as intern in the Presbyterian Hospital and the Bellevue Hospital of New York City, 1920 to 1922, and went to New Brunswick, N. J., in 1924 to begin the practice of pediatrics.

From 1924 to the time of his death, Dr. Johnson was pediatrician to the Middlesex General and St. Peter's General Hospitals. He had recently been made Treasurer of the Middlesex County Medical Society.

He was a member of the Delta Upsilon fraternity at Rutgers University, a member of Nu Sigma Nu and an honorary member of Alpha Omega Alpha at Columbia University.

Dr. Johnson is survived by his wife, the former Miss Frances Smith, daughter of the late Dr. and Mrs. A. L. Smith, and by three children.

CLARENCE L. ANDREWS, M.D., F.A.C.P.

DR. GEORGE T. HARDING, JR.

Dr. George T. Harding, Jr., son of the late Dr. George T. Harding of Marion, Ohio, and brother of the late President Warren G. Harding, died at his home in Worthington on January 18, 1934. He had been ill for ten days following a cerebral hemorrhage. Had he lived until March 11, he would have celebrated his fifty-sixth birthday.

Dr. Harding attended the Battle Creek (Michigan) College before enrolling in the University of Michigan Medical School, from which he graduated in 1900. After a few months of practice with his father, he was appointed Assistant Physician at the Columbus State Hospital, and remained there until 1906, serving as Assistant Superintendent during the last three years of his service. For two years he was Medical Superintendent of the Washington Sanitarium, Washington, D. C., and then returned to Columbus, Ohio, where he engaged in the practice of neuropsychiatry from that time until his death. His hospital connections as a Consulting Neurologist were many, and at the time of his death he was Chief of the Neurological Service at White Cross Hospital and Senior Neurologist to Grant Hospital. In 1918 he founded the Columbus Rural Rest Home, a private sanitarium for nervous and mental disorders. At various periods during his practice, he was Instructor in Neurology at the College of Medicine at Ohio State University.

In 1921 Dr. Harding was elected a Fellow of the American College of Physicians. He was active in organized medicine in its broadest sense. In 1904 he was elected a Fellow of the American Psychiatric Association and would have become a life member had he lived to attend the annual meeting this year. In 1928 he served as President of the Columbus Academy of Medicine.

His personality and ability, as well as his outstanding character, made Dr. Harding a leader in his community; his outstanding sympathy was a source of renewed hope in the lives of many who came under his care.

Dr. Harding is survived by his wife, three sons, Dr. George T. Harding, III, his associate for six years, Dr. Warren G. Harding, II, Surgeon to the Sidney Sanitarium, Sidney, Australia, Charles W. Harding, and two daughters, Mary Elizabeth and Ruth, the latter a junior student at the College of Medical Evangelists, Los Angeles.

DR. ALBERT EWALT HOFF

Dr. Albert Ewalt Hoff (Fellow), North Bend, Nebr., died January 27, 1934, from coronary thrombosis.

Dr. Hoff was born September 22, 1871, at Galesburg, Ill. The family later removed to Clarkson, Nebr. He was a graduate of Midland College, Atchison, Kansas, A.B., 1894. He received his Medical Degree in 1898 from the Central Ensworth Medical College at St. Joseph, Mo. His internship was spent at St. Joseph's Hospital, 1897–98. Over a period of more than ten years, he did postgraduate work at short intervals at the Mayo Clinic at Rochester, Minn.

He was a member and ex-president of the Dodge County Medical Association, a member of the Nebraska State Medical Association, a Fellow of the American Medical Association, and had been a Fellow of the American College of Physicians since 1928.

During his busy life, he found time for community, church and welfare work outside of his profession. He was a member of the local Board of Health, the local Board of Education, North Bend Lodge A. F. and A. M., a thirty-second degree Scottish Rite Mason, a member of the Order of the Eastern Star, a member of the I. O. O. F., and others.

Dr. Hoff had been failing in health for the last several years.

Attesting to the high regard and personal affection for Dr. Hoff, members of the Dodge County Medical Association, members of the local Masonic lodge, members of the Board of Education and the faculty of the city schools attended his funeral in a body. The schools and the business houses were closed during the hour of his funeral.

> " How oft he held the wrist to mark the slow
> Pulsations of the feebly fluttering heart,
> While his kind words, soft murmuring and low,
> Essayed to calm the mourner's pain and smart.

"He was to all a father, brother, friend;
Their joys were his, their sorrows were his own.
He sleeps in peace where yonder willows bend
Above the violets that kiss the stone."

DR. GEORGE E. McKEAN

Dr. George E. McKean, of Detroit, died February 4, 1934, of complications following a double mastoid infection. He was born at Mt. Hope, Ohio, in 1868, the son of Dr. William and Rachel McKean. His earlier education was obtained at Mt. Union College and at Northwestern Ohio Normal University. Later he attended the Medical Department of the University of Michigan where he was graduated M.D. in 1894. After three years of practice in Ohio, Dr. McKean moved to Detroit where he practised until two months before his death. He had pursued postgraduate work in London, Edinburgh, Berlin, and Munich. Dr. McKean limited his practice to internal medicine in which he had also a large consultation practice. He was attending physician at Harper Hospital for over twenty-five years, as well as consultant in medicine at the Woman's Hospital, St. Joseph Mercy Hospital, Highland Park General Hospital and the Evangelical Deaconess Hospital. Dr. McKean served in the World War fifteen months with the Harper Hospital Unit. He was director and professor of medicine of the Detroit College of Medicine. Dr. McKean was at one time president of the Detroit Medical Club and was also president and, for many years, trustee of the Wayne County Medical Society as well as member of the Michigan State and American Medical Associations, The Interstate Clinical Society and a fellow of The American College of Physicians. In 1894 Dr. McKean married Lucy E. Moore, of Ann Arbor, Michigan. He leaves, besides Mrs. McKean, three sons, Dr. Richard M. McKean, Robert E. McKean, Attorney, and Dr. Thomas McKean, all of Detroit; his mother, Mrs. Rachel McKean, Washington, D. C.; two brothers, Vice-Admiral Josiah S. McKean, U. S. N., retired, of Carmel, Calif., and John McKean, Delray, Fla.; and a sister, Mrs. James Benfer, of Washington, D. C.

Dr. McKean was much in demand in consultation by members of the medical profession of Detroit as well as throughout the State of Michigan. He was the doctor's physician. Endowed with an engaging personality, he radiated a beneficient influence in the sick room. His manner was so open and free that initial acquaintance was in many instances wont to ripen into real friendship. He lived a well-balanced life between work and play and a love of the best in literature. His three sons were his major interest and they responded well to the educational opportunities he was able to provide. As a clinical teacher, Dr. McKean had few equals, so though he has passed in the flesh, his influence lives on in the professional lives to whom he has

bequeathed a rich legacy of clinical experience. His loss is keenly felt. While called in the ripeness of his prime yet his life purpose was fulfilled. Therefore,

> Nothing is here for tears. Nothing to wail or knock the breast. No weakness or contempt, despraise or blame; nothing but well and fair, and what may quiet us in a death so noble.

JAMES D. BRUCE, M.D., F.A.C.P.